

---

# **Step Up To MRCP**

**Review Note**

**For**

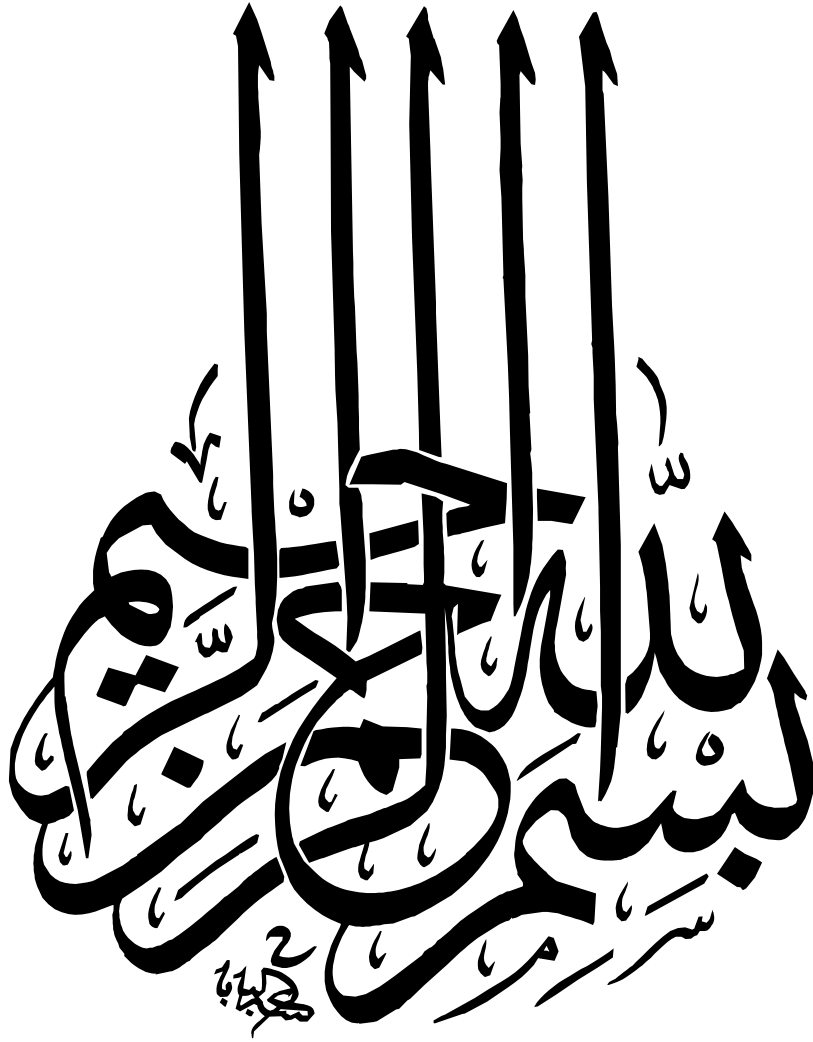
**Part I & Part II**



**By**

**Dr Khaled El Magraby**

---



---

بسم الله الرحمن الرحيم

”سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا  
إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ“

صدق الله العظيم

سورة البقرة ﴿ الآية ٣٢ ﴾

---

# Introduction

First of all, I would like to thank **ALLAH**, the most Merciful and Compassionate.

Words can never express my sincere thanks to **my parents** for everything throughout my life from **K.G** till **MRCP** and their prayers, encouragement, love, endless care and spiritual support when I was in most need of it; that can never be sufficiently acknowledged.

I pray to **ALLAH** to make this work of benefit to the all doctors would like to have MRCP by giving them the important pearls of Internal medicine and to accept our honest intention in this work.

It is a very helpful and important source for preparation and studying MRCP examination for both part 1 and 2.

It is very rich in information from many sources:

- ❖ [www.passmedicine.com](http://www.passmedicine.com)
- ❖ [www.onexamination.com](http://www.onexamination.com)
- ❖ [www.pasTest.co.uk](http://www.pasTest.co.uk)

**1<sup>st</sup> edition @ September 2015**





**دكتور خالد المغربي**  
أخصائي الأمراض الباطنة والكلية  
ماجستير الأمراض الباطنة  
كلية طب قصر العيني – جامعة القاهرة  
باحث مساعد بالمركز القومي للبحوث

**Dr Khaled El Magraby**  
Specialist of Internal Medicine & Nephrology  
M.Sc. Internal Medicine  
Cairo University, Egypt  
Assistant Researcher  
National Research Center, Egypt

**E-mail: [dr\\_khaled\\_elmagraby@hotmail.com](mailto:dr_khaled_elmagraby@hotmail.com)**

**Facebook: Khaled Elmagraby**

**00966565084114 (WhatsApp & LINE)**  
**00201223355396**

---

## **TABLE OF THE CONTENTS**

<b>Subject</b>	<b>Page</b>
<b>Chapter 1: Cardiology.....</b>	<b>1</b>
<b>Chapter 2: Pulmonology.....</b>	<b>147</b>
<b>Chapter 3: Gastroenterology &amp; Hepatology .....</b>	<b>239</b>
<b>Chapter 4: Endocrinology .....</b>	<b>341</b>
<b>Chapter 5: Haematology.....</b>	<b>473</b>
<b>Chapter 6: Nephrology.....</b>	<b>599</b>
<b>Chapter 7: Rheumatology .....</b>	<b>670</b>
<b>Chapter 8: Pharmaceuticals &amp; Therapeutics.....</b>	<b>762</b>
<b>Chapter 9: Infectious Diseases &amp; STDs.....</b>	<b>843</b>
<b>Chapter 10: Neurology.....</b>	<b>946</b>
<b>Chapter 11: Psychiatry.....</b>	<b>1054</b>
<b>Chapter 12: Ophthalmology.....</b>	<b>1084</b>
<b>Chapter 13: Dermatology.....</b>	<b>1112</b>
<b>Chapter 14: Basic Sciences, Biostatistics &amp; Miscellaneous .....</b>	<b>1158</b>

# Cardiology



### Long QT syndrome (LQTS)

LQTS is an inherited condition associated with **delayed repolarization of the ventricles**.

It is important to recognise as it may lead to **ventricular tachycardia (VT)** and can therefore cause collapse/sudden death.

The most common variants of LQTS (LQT1 & LQT2) are caused by defects in the alpha subunit of the slow delayed rectifier **potassium channel**.

A normal corrected QT interval is less than **430 ms (0.43 Sec.) in males** and **450 ms (0.45 Sec.) in females**.

Normal range for duration of the **corrected QT interval (QTc)** is **350 -430 ms**

#### Causes of a prolonged QT interval:

<u>Congenital:</u>	<u>Drugs:</u>	<u>Others:</u>
<ul style="list-style-type: none"> <li>• <b>Jervell-Lange-Nielsen (JLN) syndrome:</b> (includes <u>deafness</u> and is due to an abnormal potassium channel)</li> <li>• <b>Romano-Ward syndrome:</b> (no deafness)</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Amiodarone</b></li> <li>• <b>Sotalol</b></li> <li>• <b>Class 1a antiarrhythmic drugs.</b></li> <li>• <b>TCA</b> (e.g. amitriptyline) (&gt; SSRI)</li> <li>• <b>SSRI</b> (especially citalopram, Sertraline).</li> <li>• <b>Lithium</b></li> <li>• <b><u>Methadone</u></b></li> <li>• <b><u>Chloroquine</u></b></li> <li>• <b>Mefloquine</b></li> <li>• <b>Terfenadine</b></li> <li>• <b><u>Macrolides:</u></b> <b><u>Erythromycin,</u></b> <b><u>Clarithromycin</u></b></li> <li>• <b>Levofloxacin</b></li> <li>• <b>Domperidone</b></li> <li>• <b>Ketoconazole</b></li> <li>• <b>Haloperidol</b></li> <li>• <b>Tacrolimus</b></li> </ul>	<ul style="list-style-type: none"> <li>• <b>Electrolyte:</b> <u>Hypocalcaemia</u>, <u>Hypokalaemia</u>, <u>Hypomagnesaemia</u></li> <li>• <b>Acute MI.</b></li> <li>• <b>Myocarditis.</b></li> <li>• <b>HOCM</b></li> <li>• <u>Hypothermia.</u></li> <li>• <b>Subarachnoid haemorrhage.</b></li> <li>• <u>Hypothyroidism</u></li> </ul>

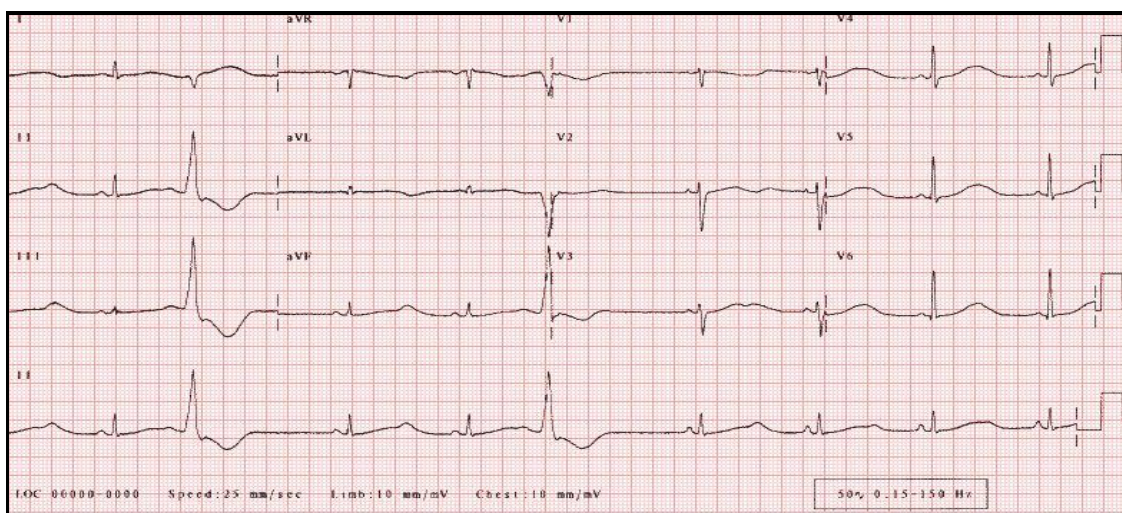
**Jervell - Lange-Nielsen (JLN) syndrome** is caused by **mutations** in the **KCNE1** and **KCNQ1** genes.

The KCNE1 and KCNQ1 genes provide instructions for making proteins that work together to form a channel across cell membranes. These channels transport positively charged **potassium** atoms (ions) out of cells. The movement of potassium ions through these channels is critical for maintaining the normal functions of **inner ear structures** and **cardiac muscle**.

### Features:

- May be picked up on routine ECG or following family screening.
- **Long QT1** - usually associated with exertional syncope, often swimming.
- **Long QT2** - often associated with syncope occurring following emotional stress, exercise or auditory stimuli e.g. doorbell or telephone ring.
- **Long QT3** - events often occur at night or at rest.
- Sudden cardiac death.
- Diagnosis is based upon the **QTc (corrected QT interval)**, although this may be within the normal range at rest; hence **Holter ECG monitoring** is recommended.
- Identification of an **LQTS genetic mutation** confirms the diagnosis. However, a negative result on genetic testing is of limited diagnostic value because **only** approximately **50%** of patients with LQTS have known mutations. The remaining half of patients with LQTS may have mutations of yet **unknown** gene.

**Therefore genetic testing of LQTS has high specificity but a low sensitivity.**



The ECG shows a long QT and ventricular premature beats. The loss of consciousness may have been due to ventricular arrhythmia, in particular, torsade de pointes VT.

**Management (by order): بالترتيب**

- 1) **Avoid drugs** which prolong the QT interval and other precipitants if appropriate (e.g. Strenuous exercise).
- 2) **Beta-blockers** (e.g. Propranolol, Metoprolol & Atenolol, **NOT Sotalol**).
- 3) **ICD** (Implantable cardioverter defibrillators) in high risk cases (i.e. It is *only* required in high risk cases, for example if the patient has a QTc > **500ms** or previous episodes of cardiac arrest).
- 4) **Left stellate cardiac ganglionectomy.**

<b>Long QT syn. &gt;&gt; usually due to loss-of-function/blockage of K<sup>+</sup> channels.</b>
--

<b>NB:</b> Beta blockers are the <b>mainstay</b> of therapy for <b>asymptomatic</b> as well as <b>symptomatic</b> patients with idiopathic LQTS.
--

Beta blockers decrease sympathetic activation from the left stellate ganglion, also decrease the maximal heart rate achieved during exertion and thereby prevent exercise-related arrhythmic events that occur in LQTS.
---

Patients who experience ventricular arrhythmias or aborted SCD despite beta blocker therapy >>> should have an **ICD** in addition to **βB**.

**Left stellate cardiac ganglionectomy** is an invasive procedure and results in Horner's syndrome. It is performed in patients who have symptoms despite βB and have frequent shocks with ICD.

**NB:** Non-sedating antihistamine and classic cause of prolonged QT in a patient, especially if also taking P450 enzyme inhibitor, e.g. Patient with a cold takes terfenadine and erythromycin at the same time.

**NB:** **Sotalol** may **exacerbate long QT syndrome** (due to blockage of K channel) it leads to a risk of ventricular arrhythmias. This can be a particular risk in individuals with **hypokalaemia**. So **Sotalol** is **better to be avoided in patients with thiazide diuretics**.

<b>EX:</b> A 75-year-old man with a history of anterior MI is taking amiodarone 400 mg/day for history of VT. He has a prolonged QTc interval on his ECG of 550 ms. The most appropriate management >>> <b>Stop amiodarone immediately and can replace with atenolol 50 mg a day.</b>
---

**Management of drug-induced LQTS is:**

- 1) **Stop** precipitating drugs.
- 2) Correction of any **electrolyte** disturbance like hypo K or Mg.
- 3) TTT of associated ventricular arrhythmia: first line for drug-induced LQTS is **IV MgSO<sub>4</sub>** 2 gm as bolus over 1-2 minutes, followed by another bolus in 15 minutes if required, or continuous infusion at a rate of 5-20 mg/min.

**QT shortening:** caused by: >>> **Hypercalcaemia, Hypermagnesaemia, Digoxin, or Thyrotoxicosis.**

**Torsade's de pointes**

Torsade's de pointes ('twisting of the points') is a rare arrhythmia associated with a long QT interval.

It may deteriorate into ventricular fibrillation and hence lead to sudden death.

Causes of long QT interval: (see before)

Risk factors: **female sex, prolonged QT interval**, bradycardia, **hypokalaemia, severe hypomagnesaemia, severe alkalosis**, CHF, digitalis toxicity, recent conversion from AF.

Management: **IV MgSo<sub>4</sub>** (Magnesium Sulphate)

MgSo<sub>4</sub> >>> it decreases Ca influx, reducing the amplitude of the VT and helping terminate runs of torsade's. It is effective even when serum magnesium level is normal.

**Ventricular tachycardia (VT): management**

Whilst a broad complex tachycardia may result from a supraventricular rhythm with aberrant conduction, the European Resuscitation Council advise that in a peri-arrest situation it is assumed to be ventricular in origin.

VT is broad-complex tachycardia originating from a ventricular ectopic focus.

It has the potential to precipitate ventricular fibrillation and hence requires urgent treatment.

There are two main types of VT:

- Monomorphic VT: most commonly caused by myocardial infarction.



- Polymorphic VT: A subtype of polymorphic VT is torsade's de pointes which is precipitated by prolongation of the QT interval.

### Management:

If the patient has adverse signs (systolic BP < 90 mmHg, chest pain, heart failure or rate > 150 beats/min) then immediate cardioversion is indicated.

In the absence of such signs antiarrhythmics may be used. If these fail, then electrical cardioversion may be needed with synchronised DC shocks.

VT with pulse (not respond to medical ttt) >>> cardioversion (**synchronized**)

Pulseless VT or VF >>> DC (**asynchronized**)

### Drug therapy:

- 1) **Amiodarone**: ideally administered through a central line (300 mg over the first hour then 900 over the next 23 hours).
- 2) **Lidocaine**: use with caution in severe left ventricular impairment as it is negative inotropic drug.
- 3) **Procainamide**.

NB: Verapamil should NOT be used in VT.

### If drug therapy fails:

- Electrophysiological study (EPS).
- Implantable cardioverter-defibrillator (ICD) - this is particularly indicated in patients with significantly impaired LV function.

NB: Hypokalaemia is the most important cause of ventricular tachycardia (VT) clinically, followed by hypomagnesaemia.

Severe hyperkalaemia may cause VT in certain circumstances, for example in patients with structural heart disease, but it is not as common a cause as hypomagnesaemia.

The 2010 ALS guidelines state that if a patient has a monitored and witnessed **VF/pulseless VT arrest** in hospital, **three quick successive (stacked) shocks 200 J** should be given. **Chest compressions should be started immediately after the third**, with a compression to ventilation ratio of **30:2 for 2 minutes**.



A **precordial thump** can be successful if given within seconds of the onset of a shockable rhythm. Delivery should not delay calling for help, or accessing a defibrillator, but would be indicated here **whilst awaiting the defibrillator**. **Chest compressions should start immediately if it is unsuccessful**.

**Adrenaline IV** would be given **every 3-5 minutes once** chest compressions had started.

**Defibrillation for three** times.

If defibrillated for the third time without return of cardiac output. CPR is immediately resumed and adrenaline administered.

The next step is **amiodarone 300 mg intravenously** (i.e. given **after the third shock**). If amiodarone is not available **lidocaine** is a suitable alternative.

**NB:** New guideline, there is no need for the 3 successive shocks, **only one shock** followed by immediate chest compression and then reassess the pulse and rhythm after finish of the cycle of 2 minutes.

**NB:** Pulseless VT with **severe hypothermia** ☹ >>> DC shock or medication will be ineffective, so better **to start with prolonged CPR firstly** till temperature can reach  $> 30^{\circ}$ . تدفئة المريض هامة جدا فى الكود بلو

Hypothermic patients do not respond well to shocks or drugs and if there is no response to the first three shocks the patient **should be rewarmed** to at least  $32^{\circ}\text{C}$  **before** any drugs or shocks are administered.

**NB:** **PVC** to be significant, they have to meet the following criteria:

- 1) Frequency  $\geq 6$  bpm.
- 2) PVC in **bigeminal** or **trigeminal** rhythm.
- 3) PVC in **short runs of VT**
- 4) PVC exhibiting **R on T phenomenon**.
- 5) PVC associated with serious **organic** heart disease and **LV decompensation**.

**Cardiac enzymes and protein markers:**

Key points for the exam:

- **Myoglobin** is the **first** to rise as early as **1 hr** of MI (within first 2 hrs), peak in 6-8 hrs and return to normal in 24 hr.
- **CK-MB** is useful to look for **re-infarction** as it returns to normal after 2-3 days (troponin T remains elevated for up to 10 days).
- **GPBB** (Glycogen phosphorylase isoenzyme BB): is an isoenzyme of glycogen phosphorylase which exists in cardiac muscle. By **three hours post myocardial infarction** it has **risen significantly**. As such it is an **appropriate marker** for **early** cardiac muscle injury.

	Begins to rise	Peak value	Returns to normal
<b>Myoglobin</b>	1-2 hours	6-8 hours	<b>1-2</b> days
<b>CK-MB</b>	2-6 hours	16-20 hours	<b>2-3</b> days
<b>CK</b>	4-8 hours	16-24 hours	3-4 days
<b>Trop T</b>	4-6 hours	12-24 hours	<b>7-10</b> days
<b>AST</b>	<b>12-24</b> hours	36-48 hours	3-4 days
<b>LDH</b>	<b>24-48</b> hours	72 hours	8-10 days

**Troponin** is a component of the **thin** filaments (along with **actin** and **tropomyosin**), and is the protein to which calcium binds to accomplish this regulation.

The other components of thin filaments are actin and tropomyosin.

Thick filaments are primarily composed of myosin.

Troponin has three subunits, TnC, TnI, and TnT.

When calcium is bound to specific sites on TnC, the structure of the thin filament changes in such a manner that myosin (a molecular motor organised in muscle thick filaments) attaches to thin filaments and produces force and/or movement.

In the absence of calcium, tropomyosin interferes with this action of myosin, and therefore muscles remain relaxed.

**Troponin T** bind to **Tropomyosin** which is a protein which regulates actin. It associates with actin in muscle fibres and regulates muscle contraction by regulating the binding of myosin.

Troponin assay at **3 and 6 hours** is adequate to determine whether myocardial damage has occurred.

<b>Causes of an elevated troponin are:</b>
--

- |   |
|---|
| <ul style="list-style-type: none"><li>➤ Trauma</li><li>➤ Cardioversion</li><li>➤ Rhabdomyolysis</li><li>➤ Pulmonary embolism</li><li>➤ Pulmonary hypertension</li><li>➤ Hypertension</li><li>➤ Hypotension, especially with arrhythmias</li><li>➤ HOCM</li><li>➤ Myocarditis including Kawasaki's disease</li><li>➤ Sepsis</li><li>➤ Burns</li><li>➤ Subarachnoid haemorrhage and stroke</li><li>➤ Infiltrative/autoimmune disorders: including sarcoidosis, amyloidosis, haemochromatosis and scleroderma.</li><li>➤ Drugs: including Adriamycin, <u>Herceptin</u> and 5-fluorouracil.</li></ul> |
|---|

### **HOCM (Hypertrophic Obstructive Cardiomyopathy)**

- HOCM is an **autosomal dominant** disorder of muscle tissue caused by defects in the genes encoding contractile proteins.
- The most common defects involve a mutation in the gene encoding β-myosin heavy chain protein or myosin binding protein C.

- Mutations to various proteins including alpha-tropomyosin and troponin T have been identified.
- The estimated prevalence is 1 in 500.
- HOCM is the most common cause of sudden cardiac death in the young.

The history of sudden arrhythmia and death in a **young, previously well**, individual is suggestive of HOCM. Relatives should be screened for it.

### **Features:**

- Often asymptomatic
- Dyspnoea, angina, syncope, palpitation
- Sudden death (commonly due to vent. arrhythmias  $\geq$ ), heart failure
- Jerky pulse, large 'a' waves,
- Double apex beat
- Ejection systolic murmur:  $\uparrow$  with Valsalva manoeuvre &  $\downarrow$  on squatting.

### **Associations:**

- Friedreich's ataxia
- Wolff-Parkinson White

### **Echo** - mnemonic - MR SAM ASH

- Mitral regurgitation (MR)
- Systolic anterior motion (SAM) of the anterior mitral valve leaflet
- Asymmetric hypertrophy (ASH): concentric hypertrophy (undilated) LV (increased septal versus LV wall diameter of ratio of  $> 1.3:1$ ).

### **ECG:**

- RBBB,
- Prolonged PR,
- Non-specific T wave abnormalities.
- L VH
- Deep Q waves in anterolateral and inferior leads
- AF may occasionally be seen

### **Cardiac catheterisation:**

Left ventricular pressures are high (210/15) with a steep drop-off between the LV and aortic systolic pressures (125/75).

**Poor prognostic factors (6):**

- 1) Syncope.
- 2) Young age at presentation.
- 3) Family history of HOCM and sudden death.
- 4) Non-sustained ventricular tachycardia on 24 or 48-hr Holter monitoring.
- 5) Abnormal blood pressure changes on exercise (drop of BP during peak exercise on stress testing).
- 6) An increased septal wall thickness > 3 cm: Septal hypertrophy causes left ventricular outflow (LVOT) obstruction. It is an important cause of sudden death in apparently healthy individuals.

**Management (ABCDE):**

- 1) Amiodarone
- 2) **Beta-blockers**
- 3) Cardioverter defibrillator (ICD)
- 4) **Dual chamber pacemaker**
- 5) **Endocarditis prophylaxis\***

N.B: Reducing outflow tract obstruction with **myomectomy** or alcohol septal ablation does **not** reduce the risk of SCD, but it is usually recommended especially when the **outflow gradient is greater than 50 mmHg particularly if symptoms of dyspnoea persist post  $\beta$  blockade.**

**Drugs to avoid:**

- Nitrates
- ACE-inhibitors
- Inotropes

**NB:** Verapamil should however be avoided in HOCM patients with coexistent Wolff-Parkinson White as it may precipitate VT or VF.

**NB:** Most cardiologists would now proceed to inserting an implantable cardioverter defibrillator (ICD) to lower the risk of sudden cardiac death (SCD).

**EX:** Pt. HOCM with palpitations >>> a 24 hour ECG reveals >>> runs of non-sustained VT >>> best ttt is ICD.

**NB: The most common causes of sudden cardiac death (SCD):**

- **HOCM** is a more common cause of sudden cardiac death than arrhythmogenic right ventricular dysplasia (ARVD). The estimated prevalence is 1 in 500.

- **ARVC** (Arrhythmogenic right ventricular cardiomyopathy): the second most common cause of sudden cardiac death in the young after HOCM.
- **CPVT** (Catecholaminergic polymorphic ventricular tachycardia) is a form of inherited cardiac disease. It is inherited in an autosomal dominant fashion and has a prevalence of around 1:10,000.
- **Brugada syndrome** is a form of inherited cardiovascular disease. It is inherited in an autosomal dominant fashion and has an estimated prevalence of 1:5,000-10,000. Brugada syndrome is more common in Asians.

### **Screening of HOCM:**

Current guidelines suggest that a **resting ECG** and **TTE (transthoracic ECHO)** are the **most effective** screening strategies for relatives of patients with HOCM.

**Genetic** testing is **not** recommended as a first line screening tool given varying rates of penetrance.

### **Arrhythmogenic right ventricular cardiomyopathy (ARVC)**

It is a form of inherited CV disease which may present with syncope or SCD.

It is generally regarded as the **second** most common cause of sudden cardiac death in the young after HOCM.

### **Pathophysiology:**

- Inherited in an autosomal dominant pattern with variable expression
- The right ventricular myocardium is replaced by fibrofatty tissue

### **Presentation:**

- Palpitations
- Syncope
- Sudden cardiac death

### **Investigation:**

- **ECG** abnormalities in V1-3, typically T wave inversion. An epsilon wave is found in about 50% of those with ARVC - this is best described as a terminal notch at the end of QRS complex.



- **Echo** changes are often subtle in the early stages but may show an enlarged, hypokinetic right ventricle with a thin free wall.
- **MRI** is useful to show fibrofatty tissue.

#### **Management:**

- Beta-blockers: sotalol is the most widely used antiarrhythmic
- Catheter ablation to prevent ventricular tachycardia
- Implantable cardioverter-defibrillator

#### **NB: Naxos disease:**

- An autosomal recessive variant of ARVC
- A triad of ARVC + palmo-plantar keratosis+ and woolly hair.

#### **Catecholaminergic polymorphic ventricular tachycardia (CPVT)**

CPVT is a form of inherited cardiac disease associated with SCD.

It is inherited in an autosomal dominant fashion and has a prevalence of around 1:10,000.

#### **Pathophysiology:**

- The most common cause is a defect in the ryanodine receptor (RYR2) which is found in the myocardial sarcoplasmic reticulum.

#### **Features:**

- Exercise or emotion induced polymorphic ventricular tachycardia resulting in syncope.
- Sudden cardiac death.
- **Symptoms generally develop before the age of 20 years.**

#### **Management:**

- Beta-blockers
- Implantable cardioverter-defibrillator (ICD).

**Brugada syndrome (Br S) (Brugada et al., 1992)**

Brugada syndrome is a form of inherited cardiovascular disease with may present with sudden cardiac death.

It is inherited in an autosomal dominant fashion and has an estimated prevalence of 1:5,000-10,000.

Brugada syndrome is more common in Asians.

**Pathophysiology:**

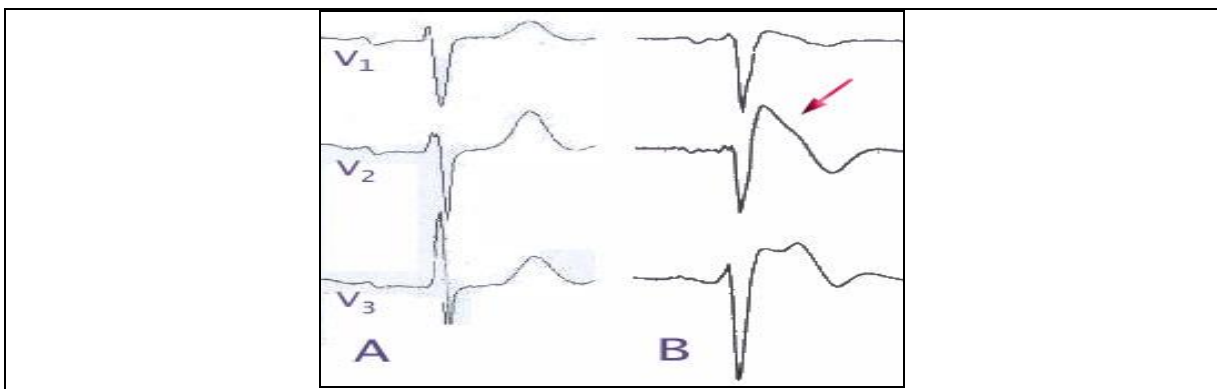
- A large number of variants exist.
- Around 20-40% of cases are caused by a mutation in the **SCN5A gene** which encodes the myocardial sodium ion channel protein.
- Usually there are no structural abnormalities in Brugada syndrome patients and the disease may be defined as **a pure electrical abnormality** of myocardial cells (i.e. Normal Echo).
- Usually manifests with syncope or SCD occurring in the third or fourth decade of life and usually at rest or during sleep.

**Investigations:**

- 1) **ECG** changes:
  - a) Convex ST elevation V1-V3
  - b) Complete or incomplete right bundle branch block (RBBB)
  - c) Changes may be more apparent following Flecainide.
- 2) **IV ajmaline with electrophysiological study (EPS) testing.**

**Management:**

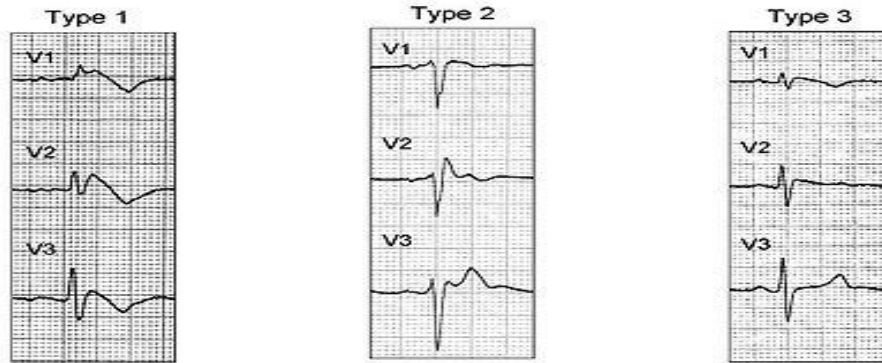
No ttt apart from prophylactic insertion of Implantable cardioverter-defibrillator (**ICD**) aiming to treat life threatening arrhythmia esp. VT.



(A) Normal ECG in the precordial leads V<sub>1-3</sub>,

(B) Brugada syndrome (type B).



**NB: Brugada syndrome (3 types):**

- **Type 1** has a coved type ST elevation with at least 2 mm (0.2 mV) J-point elevation a gradually descending ST segment followed by a negative T-wave.
- **Type 2** has a saddle back pattern with a least 2 mm J-point elevation and at least 1 mm ST elevation with a positive or biphasic T-wave. Type 2 pattern can occasionally be seen in healthy subjects.
- **Type 3** has either a coved (type 1 like) or a saddle back (type 2 like) pattern with less than 2 mm J-point elevation and less than 1 mm ST elevation. Type 3 pattern is not uncommon in healthy subjects.

**Hypertension in pregnancy**

Women who are at high risk of developing pre-eclampsia should take aspirin 75mg OD from 12 weeks until the birth of the baby.

High risk groups include:

- Hypertensive disease during previous pregnancies
- Type 1 or 2 diabetes mellitus
- Chronic kidney disease
- Autoimmune disorders such as SLE or Antiphospholipid syndrome

The classification of hypertension in pregnancy is complicated and varies.

**Remember, in normal pregnancy:**

- **Blood pressure** usually **falls in the first trimester** (particularly the **diastolic**), and **continues to fall until 20-24 weeks.**
- **After this time** the blood pressure **usually increases to pre-pregnancy levels by term.**

- The **heart rate increases** by 10-20 bpm, **stroke volume** and **cardiac output increase** but venous pressure should remain the same due to a 25% reduction in systemic and pulmonary vascular resistance.

Blood pressure during pregnancy normally falls in first half of pregnancy before rising to pre-pregnancy levels before term.

**Hypertension in pregnancy is usually defined as:**

- Systolic > 140 mmHg or diastolic > 90 mmHg.**
- Or an increase above booking readings of > 30 mmHg systolic or > 15 mmHg diastolic.**

After establishing that the patient is hypertensive they should be categorised into one of the following groups:

Pre-existing hypertension (Chronic HTN)	Pregnancy-induced hypertension (PIH),  also known as (Gestational hypertension)	Pre-eclampsia
<ul style="list-style-type: none"> <li>➤ A history of hypertension <b><u>before pregnancy</u></b> or an elevated blood pressure &gt; 140/90 mmHg <b><u>before 20 weeks gestation.</u></b></li> <li>➤ <b>No</b> proteinuria, no oedema.</li> </ul> <p>Occurs in 3-5% of pregnancies and is more common in older women.</p>	<ul style="list-style-type: none"> <li>➤ Hypertension (as defined above) occurring in the second half of pregnancy (i.e. <b><u>after 20 Wks</u></b>).</li> <li>➤ <b>No</b> proteinuria, no oedema</li> <li>➤ Occurs in around 5-7% of pregnancies.</li> <li>➤ Resolves following birth (typically after one month).</li> <li>➤ Women with PIH are at increased risk of future pre-eclampsia or HTN later in life.</li> </ul>	<ul style="list-style-type: none"> <li>➤ Pregnancy-induced hypertension after 20 wks. in association with <b><u>proteinuria</u></b> (&gt;0.3g / 24 hours)</li> <li>➤ <u>Oedema</u> may occur but is now less commonly used as a criteria.</li> </ul> <p>Occurs in around <b>5%</b> of pregnancies.</p>

**NB:** Pregnancy related blood pressure problems (such as pregnancy-induced hypertension or pre-eclampsia) do not occur before 20 weeks.

**NB:** The raised ambulatory blood pressure readings exclude a diagnosis of white-coat hypertension.

**NB:** The **target BP** in patients with **pre-existing hypertension** is **under 150/100 mmHg**, or 140/90 mmHg in the presence of end organ failure.

As in patients with longstanding HTN aggressive BP control may compromise placental function, so **diastolic blood pressure should be preserved > 80 mmHg**. Any increase in BP above baseline should prompt a search for new pre-eclampsia.

### **Pre-eclampsia:**

Pre-eclampsia is a condition seen after 20 weeks gestation characterised by pregnancy-induced hypertension in association with proteinuria (> 0.3g / 24 hours). Oedema used to be third element of the classic **triad** but is now often not included in the definition as it is not specific.

Pre-eclampsia is defined as:

- 1) Condition seen after 20 weeks gestation
- 2) Pregnancy-induced hypertension (PIH)
- 3) Proteinuria

Pre-eclampsia is important as it predisposes to the following problems:

- Fetal: prematurity, intrauterine growth retardation
- Eclampsia
- Haemorrhage: placental abruption, intra-abdominal, intra-cerebral
- Cardiac failure
- Multi-organ failure

### **Risk factors:**

- 1) **> 40 years old**
- 2) **Null parity** (or new partner)
- 3) **Multiple pregnancy (twins)**
- 4) Pregnancy **interval** of more than 10 years
- 5) **BMI > 30 kg/m<sup>2</sup>**
- 6) **DM**
- 7) **Family history** of pre-eclampsia
- 8) **Previous history** of pre-eclampsia
- 9) **Pre-existing vascular** disease such as hypertension or renal disease

Some evidences suggest that pre-eclampsia is less common in smokers ☺

**Features of severe pre-eclampsia:**

- **Hypertension:** typically > **170/110** mmHg
- **Proteinuria:** dipstick ++/+++
- **Headache**
- Visual disturbance, **Papilledema**
- **Hyperreflexia, clonus**
- **RUQ/epigastric pain**
- **HELLP syndrome:** Haemolysis, Elevated Liver enzymes, Low Platelet count <  $100 \times 10^6/l$ .

Nearly 10% of women with severe preeclampsia and 30-50% of women with eclampsia are affected by HELLP syndrome.

The exact relationship between HELLP syndrome and Pre-eclampsia is unknown.

**One third** of women with **pre-eclampsia (HELLP)** develop **DIC or TTP**.

**Management:**

**Pre-eclampsia >>> best and definitive ttt is >>> Delivery of the baby.**

- Patients with chronic hypertension are at increased risk of developing pre-eclampsia and are therefore prescribed **75 mg of aspirin daily from 12 weeks**, which is believed to reduce the risk.
- Consensus guidelines recommend treating blood pressure > 160/110 mmHg although many clinicians have a lower threshold.
- **Oral / IV labetalol** is now **first-line** following the 2010 NICE guidelines.
- Nifedipine, or hydralazine can be used as alternatives after considering side-effect profiles for the woman, foetus and new-born baby.
- **Delivery of the baby** is the **most** important and **definitive** management step. The timing depends on the individual clinical scenario.
- **MgSo4** is used **peri-delivery** to reduce the risk of seizures, and may have adjunctive effects on lowering BP and would be considered as the potential next step after BP lowering by IV labetalol. (**Firstly Labetalol IVI then MgSo4 IVI**).

**EX:** Pregnant female 35 week with BP 180/130 mmHg, severe headache, blurring of vision, bilateral LL oedema, bilateral papilledema >>> Next step is **firstly IV labetalol, then MgSo4 IVI peri-delivery**.

**Labetalol oral** is **first line** for **moderate hypertension** in **pregnancy**, according to NICE guidance.

**TTT of HTN in pregnancy:**

**Safe:** 😊

- Labetalol,
- Nifedipine,
- Aldomet (max dose 1 gm BID),
- Hydralazine

**Not safe** ☹️

- ACEI / ARBs (risk of renal agenesis and subsequent fetal death) and
- Diuretics (↓ volume expansion associated during normal pregnancy) are absolutely contraindicated.
- Atenolol is associated with IUGR and so it is not the first choice beta blocker for use in pregnancy, in contrast Labetalol is not associated with IUGR.

**TTT of hyperemesis:**

First line: **Promethazine** is recommended in the BNF as a potential 1st line ttt.

Alternative include Domperidone and Ondansetron.

Metoclopramide and prochlorperazine are associated with increased risk of acute dystonia in young women, therefore they are only recommended in guidelines in the second line position for the ttt of symptoms of hyperemesis.

## Eclampsia

**Eclampsia** is the development of **seizures** in association **pre-eclampsia**.

Eclampsia >>> Give magnesium sulphate first-line

**Magnesium sulphate (MgSO<sub>4</sub> IVI)** is used to **both prevent** seizures in patients with severe pre-eclampsia and **treat** seizures once they develop.

Guidelines on its use suggest the following:

- Should be given **once** a decision to delivery has been made.
- In eclampsia an **IV bolus of 4g over 5-10 minutes** should be given **followed by an infusion of 1g / hour**.
- Treatment should **continue for 24 hours** after last seizure or delivery (around 40% of seizures occur post-partum).
- Follow up and monitoring of the following **4 items during intake** of MgSO<sub>4</sub> IVI infusion:
  - 1) **Urine output,**
  - 2) **Reflexes,**
  - 3) **Respiratory rate** and
  - 4) **Oxygen saturations.**

Other important aspects of treating severe pre-eclampsia/eclampsia include **fluid restriction** to avoid the potentially serious consequences of fluid overload.

### **NB: PPCM (peri-partum cardiomyopathy):**

Peripartum cardiomyopathy is a dilated cardiomyopathy of uncertain aetiology occurring in the last month of pregnancy or within 5 months after delivery. Symptoms are the same as those of cardiac failure in non-pregnant patients. In order to make the diagnosis there must be (1) absence of any other cause for the cardiac failure, (2) absence of heart disease before the last month of pregnancy, and (3) documented systolic dysfunction. Pre-eclampsia is an important differential and must be excluded. A history of visual disturbance, headache, abdominal pain and peripheral oedema along with hyperreflexia, clonus, right-upper-quadrant tenderness, renal impairment and proteinuria all suggest pre-eclampsia. Treatment is the same as for the non-pregnant patient with cardiac failure, although angiotensin-converting enzyme inhibitors should be avoided. The mainstay of medical treatment is digoxin and loop diuretics. If indicated nitrates and inotropic support with dobutamine should be used.

**Atrial fibrillation: classification**

An attempt was made in the joint American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) 2012 guidelines to simplify and clarify the classification of atrial fibrillation (AF).

It is recommended that AF be classified into 3 patterns:

- 1) **First detected episode** (irrespective of whether it is symptomatic or self-terminating).
- 2) **Recurrent** episodes, when a patient has 2 or more episodes of AF. If episodes of AF terminate spontaneously then the term **paroxysmal AF** is used. Such episodes last less than 7 days (typically < 24 hours). If the arrhythmia is not self-terminating then the term **persistent AF** is used. Such episodes usually last greater than 7 days.
- 3) In **permanent AF** there is continuous atrial fibrillation which cannot be cardioverted or if attempts to do so are deemed inappropriate. Treatment goals are therefore rate control and anticoagulation if appropriate.

**NB:** Supraventricular arrhythmias secondary to acute alcohol intake are well characterised and have been termed 'holiday heart syndrome'. No specific treatment is required.

**Atrial fibrillation: anticoagulation**

The European Society of Cardiology (ESC) published updated guidelines on the management of atrial fibrillation in 2012.

They suggest using the **CHA<sub>2</sub>DS<sub>2</sub>-VASc** score to determine the most appropriate anticoagulation strategy. This scoring system superseded the CHADS<sub>2</sub> score.

	Condition	Points
<b>C</b>	Congestive heart failure	1
<b>H</b>	Hypertension (or treated hypertension)	1
<b>A<sub>2</sub></b>	Age ≥ 75 years	2
<b>D</b>	Diabetes	1
<b>S<sub>2</sub></b>	Prior Stroke or TIA	2
<b>V</b>	Vascular disease (including IHD and PVD)	1
<b>A</b>	Age 65-74 years	1
<b>S</b>	Sex (female)	1
<b>( CH A<sub>2</sub> D S<sub>2</sub> VAS ) total score</b>		<b>10</b>

The table shows a suggested anticoagulation strategy\* based on the score:

Score	Anticoagulation
0	No treatment is preferred to <u>aspirin</u>
1	<u>Oral anticoagulants</u> preferred to aspirin; ( <u>Dabigatran</u> is an alternative)
≥ 2	<u>Oral anticoagulants</u> ; ( <u>Dabigatran</u> is an alternative)

**\*NB:** The wording in the guidelines ('is preferred to') can be slightly confusing. It basically means that, say for a score of 0, whilst aspirin is an acceptable management option the weight of the clinical evidence would support no treatment instead.

**NB:** However, the following are conditions that, if present, may trump the decision to **anticoagulate**:

- 1) Valvular heart disease (Mitral Stenosis)
- 2) Prior peripheral embolism, and
- 3) Intracardiac thrombus.

**Paroxysmal AF (PAF):** the patient should be **warfarinised** as the patient is at significant risk of an embolic stroke.

Also for anti-arrhythmic like **beta blocker; Bisoprolol** (it is the treatment of choice if there are no contraindications as achieve rate control during the PAF episode, beneficial for BP control, for LV impairment, beneficial for IHD).

**Sotalol** though effective treatment for paroxysmal AF is potentially pro-arrhythmic (increases risk of torsades by prolonging QT) and does not cardiovert AF but can help to maintain sinus rhythm.

**Esmolol IV** is a short acting  $\beta$ B used in ttt of paroxysmal SVT.

**Flecainide IV** is a good **chemical cardioversion** agent especially with PAF related to **alcohol** excess, but it is **contraindicated** in patients with structural heart disease and at high risk of IHD. Also it can be used in **atrial flutter**.

**Diltiazem** is rate limiting but is generally used in beta blocker intolerant patients.

**Amiodarone** is the typical second line choice, but is not the usual first line choice and should be reserved for refractory cases due to its wide side effects profile.

**Digoxin** has little value in Paroxysmal AF.



**NB:** In patient with atrial fibrillation and as a consequence he has had a **number of transient ischaemic attacks (TIAs) and with NORMAL CT Brain** >>> hence he is in needs to be anticoagulated immediately with warfarin.

**But** in AF patients who've had an **ischaemic stroke** >>> the guidelines recommend waiting 2 weeks before anticoagulation is commenced to reduce the risk of haemorrhagic transformation.

So NICE recommends for **AF** patients with **TIA**: >>> **Do CT BRAIN**:

- In the absence of cerebral infarction or haemorrhage >>> anticoagulation therapy should begin as soon as possible.
- In the presence of ischaemic stroke >>> wait two weeks before start anticoagulation.

Compared to a person in sinus rhythm, a patient with **AF** has a **5 folds** increased risk of **stroke**. Stroke mortality is also higher than those without AF.

**NB:** Patient with AF then developed **blindness** >>> so extensive bilateral **occipital lobe infarction** as a result of emboli shower. Neuroimaging should be urgently performed to confirm the diagnosis. The pupillary response will be preserved in this case.

### **Dabigatran (Pradaxa ®):**

It is oral anticoagulant, **anti- thrombin (factor 2)**

The drug dabigatran has a **half-life elimination of 12-14 hours** in normal subjects; it lasts **longer** in patients with abnormal **kidney** function.

Dabigatran **should be stopped before colonoscopy:-**

For patients with **normal** creatinine clearance, it is safe to **discontinue the drug 1 to 2 days before colonoscopy procedure**.

For the patient with **CKD**, it is better **to stop the drug 3 to 5 days before the procedure**. An even longer period might be considered for those undergoing major surgery, spinal puncture or placement of epidural catheter (in whom complete haemostasis is warranted).

The drug contributes to INR elevation but its effect cannot be monitored in such manner. Similarly, use of **aPTT** can only provide an approximation of **dabigatran's anticoagulant activity**.

It should be noted that there is **absence of antidote** to reverse rapidly the anticoagulant effects of dabigatran in the case of life-threatening haemorrhage or surgery.

**Haemodialysis** removes around **60%** of the drug over 2 to 3 hours.

**NB:** Clearance of the **LMHH** is **predominantly** by **renal** route.

**NB:** **Unfractionated heparin's half-life** is not affected by renal function; it is metabolised by hepatic and vascular endothelial heparinases. So it is **very safe** with no adjusted dose for **renal** patients.

Warfarin should be taken about **the same time each day**, if the patient forgot to take her warfarin last day, **she should take it later that day**, and she should **not take a double dose the next day**. She should make a note and let the anticoagulation clinic know when she attends.

### **Atrial fibrillation: cardioversion**

#### **Onset < 48 hours:**

If the AF is definitely of less than 48 hours onset patients should be heparinised. Patients who have risk factors for ischaemic stroke should be put on lifelong oral anticoagulation. Otherwise, patients may be cardioverted using either:

- **Electrical** - 'DC cardioversion'
- **Pharmacology:**
  - Amiodarone if structural heart disease,
  - Flecainide in those without structural heart disease or IHD.
  - Others (less commonly used in UK): quinidine, dofetilide, ibutilide, propafenone.
  - Less effective agents:
    - $\beta$ B (sotalol), CCBs, Digoxin, Disopyramide, Procainamide

Following electrical cardioversion if AF is confirmed as being less than 48 hours duration then further anticoagulation is unnecessary

### Onset > 48 hours:

If the patient has been in AF for more than 48 hours then anticoagulation should be given for at least **3 weeks prior to cardioversion**. An alternative strategy is to perform a transoesophageal echo (TOE) to exclude a left atrial appendage (LAA) thrombus. If excluded patients may be heparinised and cardioverted immediately.

If there is a high risk of cardioversion failure (e.g. previous failure or AF recurrence) then it is recommended to have at least 4 weeks amiodarone or sotalol prior to electrical cardioversion.

Following electrical cardioversion patients should be **anticoagulated for at least 4 weeks**. After this time decisions about anticoagulation should be taken on an individual basis depending on the risk of recurrence (CHADS score).

If the patient is **haemodynamically compromised** due to **AF** whatever the cause >>> the emergency ttt is **DC cardioversion: 200 J ⇒ 360 J ⇒ 360 J**.

Adverse signs necessitating DC cardioversion are:

- 1) **SBP ≤90 mmHg**
- 2) **Heart rate ≥200 bpm.**
- 3) Impaired consciousness (**confusion**)
- 4) **Chest pain**
- 5) **Heart failure**

If it is certain the AF has been present **for two days or less**, cardioversion can be attempted (electrical or pharmacological). Warfarin is **not** required if cardioversion is successful.

If present for **more than two days**, warfarin is given for **at least 3 weeks before** cardioversion is attempted, and **continued for at least 4 weeks following**. Continuing warfarin should be considered for patients at high risk of recurrence (large left atrium, poor LV function, and HTN) or previously symptomatic AF.

### **Atrial fibrillation: rate control and maintenance of sinus rhythm**

The Royal College of Physicians and NICE published guidelines on the management of AF in 2006. The following is also based on the joint American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) 2012 guidelines.

Agents used to **control rate** in patients with AF:

- 1) Beta-blockers (e.g. Atenolol).
- 2) Calcium channel blockers (NOT Amlodipine).
- 3) Digoxin (not considered first-line anymore as they are less effective at controlling the heart rate during exercise. However, they are the preferred choice if the patient has coexistent heart failure).

Agents used to **maintain sinus rhythm** in patients with a history of AF:

- 1) **Amiodarone**.
- 2) Flecainide.
- 3) Sotalol.
- 4) Others (less commonly used in UK): disopyramide, dofetilide, procainamide, propafenone, quinidine.

**Amiodarone** has been shown to be superior in maintaining sinus rhythm following successful DC cardioversion of AF, however, it is associated with more toxic side effects than the other agents mentioned.

The table below indicates some of the factors which may be considered when considering either a **rate** control or **rhythm** control strategy:

Factors favouring <u>rate</u> control	Factors favouring <u>rhythm</u> control
<ul style="list-style-type: none"> <li>➤ <u>Older</u> than 65 years.</li> <li>➤ History of <u>IHD</u>.</li> </ul>	<ul style="list-style-type: none"> <li>➤ <u>Younger</u> than 65 years.</li> <li>➤ <u>Symptomatic</u>.</li> <li>➤ <u>First</u> presentation.</li> <li>➤ <u>Lone</u> AF or AF <u>secondary</u> to a <u>corrected</u> precipitant (e.g. <u>Alcohol</u>).</li> <li>➤ <u>Congestive heart failure (CHF)</u>.</li> </ul>

Patients under 75 with mitral valve prolapse (MVP) who are in atrial fibrillation or those who have echocardiographic evidence of left ventricular impairment should be referred for surgical assessment as early as possible. A TOE (Transoesophageal Echocardiogram) can demonstrate whether the valve is amenable to repair or needs replacement. This is often performed intra-operatively. Progressive mitral regurgitation is the most serious complication occurring in about 15% of patients over a 15-year period. Acute hemiplegia, transient ischaemic attacks, cerebellar infarcts, amaurosis fugax and retinal arterial occlusions all occur more frequently in MVP patients, suggesting that cerebral emboli are actually quite common in this condition.

**Amiodarone (Cordarone®)**

Amiodarone is a **class III antiarrhythmic agent** used in the treatment of atrial, nodal and ventricular tachycardias.

The main mechanism of action is by **blocking potassium channels** which inhibits repolarisation and hence prolongs the action potential.

It also has other actions such as **blocking sodium channels** (a class Ia effect).

Amiodarone is considered as <b>both class Ia</b> and class <b>III</b> .
---

The use of amiodarone is limited by a number of factors:

- **Long half-life (20-100 days).**
- Should ideally be given into central veins (causes **thrombophlebitis**).
- Has **proarrhythmic** effects due to **lengthening of the QT interval**.
- **Interacts** with drugs commonly used concurrently e.g. decreases metabolism of warfarin (**P450 inhibitor**), so ↑ bleeding.
- Numerous long-term adverse effects (see below).

Monitoring of patients taking amiodarone:

- TFT, LFT, U&E, CXR prior to treatment.
- TFT, LFT every 6 months.

Adverse effects of amiodarone use:

- Thyroid dysfunction: (Hypothyroidism in 30% and thyrotoxicosis in 15%)
- **Corneal deposits**: in at least **90%** of cases.
- Pulmonary **fibrosis**/pneumonitis (in 5%)
- Liver fibrosis/hepatitis (less than 5%)
- Peripheral neuropathy, myopathy
- Photosensitivity rash (rash on the forearms and face): can use sun block
- **'Slate-grey' appearance**
- Thrombophlebitis and injection site reactions
- Bradycardia

NB: All antiarrhythmic drugs have the potential to cause arrhythmias. Coexistent **hypokalaemia** significantly increases this risk.

So should checking the urea and electrolytes prior to commencing a patient on amiodarone.

**NB:** Amiodarone toxicity occurs in approximately **5%** of patients. This can vary from **acute respiratory distress** to a picture of **cough, pleuritic chest pain, pulmonary infiltrates** and small **pleural effusions** to **interstitial pneumonitis** and eventually **progressive pulmonary fibrosis**.

Due to its **long half-life**, amiodarone toxicity takes some **weeks to resolve**; as such **corticosteroids** are added when therapy is discontinued as this may lead to more rapid resolution of symptoms.

### Amiodarone and the thyroid gland

**Around 1 in 6** patients taking amiodarone develop thyroid dysfunction.

The incidence of amiodarone induced thyroid dysfunction has **no** relationship at all to photosensitivity.

Bizarre thyroid function tests (TFTs) seem to feature at the MRCP exam and amiodarone is usually the cause.

Amiodarone contains **75 mg of iodine** per 200 mg tablet.

In addition, the **half-life is very long (100 days)** and can result in prolonged effects even after stopping therapy for several months.

#### **Amiodarone-induced hypothyroidism (AIH):**

The pathophysiology of amiodarone-induced hypothyroidism (AIH) is thought to be due to the high iodine content of amiodarone causing a **Wolff-Chaikoff effect** (it is an auto regulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide). **Iodine driven inhibition of thyroid hormone synthesis.**

**Amiodarone may be continued** if this is desirable especially in cases of VT it would be unwise to withdraw amiodarone abruptly. So **continue amiodarone and add thyroxine.**

The **typical results** of amiodarone-induced hypothyroidism which inhibits the peripheral conversion of T4 to T3 is >>>>

↑TSH, low T3 and normal or elevated T4.

As T3 is the most active thyroid hormone, the low T3 feedbacks at the pituitary level result in increased TSH secretion.

### Amiodarone-induced thyrotoxicosis (AIT):

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

	AIT type 1	AIT type 2
Pathophysiology	Accelerated thyroid hormone synthesis secondary to <b>iodide load. (Jod-Basedow effect)</b> .  Occurs in patients <b>with</b> underlying latent thyroid pathology.	Amiodarone-related <b>destructive thyroiditis</b> with direct effect of amiodarone on the follicular cells, with breakdown of cells and therefore <b>release of preformed</b> thyroid hormones T4 and T3.  This is a <b>direct</b> toxic effect of amiodarone on the thyroid follicular cells, and occurs in patients <b>without</b> underlying thyroid disease.  Clinically <b>neck tenderness</b> .
Goitre	<b>Present</b>	Absent
<b>Duplex US on thyroid for blood flow</b>  (is the most useful to differentiate between both types) 😊	<b>Increase</b>	Decrease
<b>Iodine-131 uptake scan</b>	<b>Normal or high</b>	Low or none

	AIT type 1	AIT type 2
Thyroid autoantibodies	Positive	
IL-6		High IL-6
Management	<b>Carbimazole</b> 40 mg OD or <b>K perchlorate</b> or <b>lithium carbonate</b> or <b>Surgery</b>	Corticosteroids <b>(prednisolone 40 mg/d)</b>

Unlike in AIH, **amiodarone should be stopped** if possible in patients who develop **AIT**.

And if necessary **other anti-arrhythmic** could be used to maintain sinus rhythm such as sotalol or flecainide (if not contraindicated).

**If** amiodarone cannot be withdrawn then **total thyroidectomy** should be considered.

### Flecainide

Flecainide is a Vaughan Williams class **1c** antiarrhythmic.

It slows conduction of the action potential by acting as a potent **sodium channel blocker**.

This may be reflected by **widening of the QRS complex** and **prolongation of the PR interval**.

Indications:

- 1) **Atrial fibrillation.**
- 2) SVT associated with accessory pathway e.g. **WPW syndrome.**



Adverse effects:

- 1) Negatively inotropic
- 2) Bradycardia
- 3) Proarrhythmic
- 4) Visual disturbances
- 5) Oral paraesthesia

Contraindicated:

- 1) **Structural** heart disease.
- 2) **Ischemic** heart disease

The Cardiac Arrhythmia Suppression Trial (CAST, 1989) investigated the use of agents to treat asymptomatic or mildly symptomatic premature ventricular complexes (PVCs) post MI. The hypothesis was that this would reduce deaths from ventricular arrhythmias. Flecainide was actually shown to **increase mortality post MI** and is therefore **contraindicated** in this situation.

#### **DVLA: cardiovascular disorders**

The guidelines below relate to car/motorcycle use unless specifically stated.

For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter.

Specific rules:

- **Hypertension** - can drive unless treatment causes unacceptable side effects, no need to notify DVLA. If Group 2 Entitlement the disqualifies from driving if resting BP consistently 180 mmHg systolic or more and/or 100 mm Hg diastolic or more.
- **Angioplasty (elective)** - 1 week off driving.
- **CABG** - 4 weeks off driving.
- **Acute coronary syndrome**- 4 weeks off driving, 1 week if **successfully treated by angioplasty**.
- Angina - driving must cease if symptoms occur at rest/at the wheel.
- **Pacemaker insertion** - 1 week off driving.
- **Implantable cardioverter-defibrillator (ICD)**: if implanted for sustained ventricular arrhythmia: cease driving for 6 months. If implanted prophylactically then cease driving for 1 month.
- Successful catheter ablation for an arrhythmia- 2 days off driving

- Aortic aneurysm of 6cm or more - notify DVLA. Licensing will be permitted subject to annual review. An aortic diameter of 6.5 cm or more disqualifies patients from driving
- **Heart transplant:** DVLA do not need to be notified

**EX:** Pt with post MI and had received thrombolytic therapy >>> he has to stop driving, inform the DVLA, and return for **exercise ECG test in 6 weeks** while **off all anti-angina medications as  $\beta$  blocker** (not ASA or Plavix) for **48** hours before. There should be **no residual chest pain or significant ECG changes**.

### Infective endocarditis

The strongest risk factor for developing infective endocarditis **is a previous episode of endocarditis**.

The following types of patients are affected:

- Previously normal valves (50%, typically acute presentation)
- Rheumatic valve disease (30%)
- Prosthetic valves
- Congenital heart defects
- Intravenous drug users (IVDUs, e.g. Typically causing tricuspid lesion)

Causes:

- **Streptococcus viridans** (most common cause - 40-50%)
- Staphylococcus aureus (coagulase **positive** +ve) (especially acute presentation, IVDUs).
- Staphylococcus epidermidis (coagulase **negative** -ve) (especially prosthetic valves).
- Streptococcus bovis is associated with colorectal cancer.
- Streptococcus mitis (viridans streptococcus): following dental work.
- Non-infective: SLE (Libman-Sacks), malignancy (**marantic endocarditis**): **(Non-bacterial thrombotic endocarditis)**.

Culture negative causes:

- Prior antibiotic therapy
- Brucella
- Bartonella
- Coxiella burnetii
- HACEK: Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella)

**NB:** Following prosthetic valve surgery **Staphylococcus epidermidis** is the most common organism in the first 2 months and is usually the result of perioperative contamination.

After 2 months the spectrum of organisms which cause endocarditis return to normal, except with a slight increase in Staph aureus infections.

Most common cause of endocarditis:

- **Streptococcus viridans.**
- **Staphylococcus epidermidis** if < 2 months post valve surgery.

**NB:** EX. Pt. with sigmoid adenocarcinoma + fever + SOB >>> Echo >>> IEC (*Streptococcus bovis*).

**NB:** **Coxiella** infection is widespread in **domestic and farm animals**, it usually spreads between animals by ticks which acts as reservoirs of infection.

Infection may be spread via unpasteurised milk.

Coxiella is usually diagnosed via **complement fixation**.

TTT: **Doxycycline**

A dangerous complication of **Aortic valve endocarditis** that it can cause **aortic root abscess** which can cause damage/ erosion to the **AV node** resulting in **prolongation of the PR interval** on 12 lead ECG.

So **ECGs** should be performed **daily** to monitor for infections involving the aortic root/aortic valve.

### **Infective endocarditis: Modified Duke Criteria**

Infective endocarditis diagnosed if:

- Pathological criteria positive, or
- 2 major criteria, or
- 1 major and 3 minor criteria, or
- 5 minor criteria

**Pathological criteria:**

Positive histology or positive microbiology of pathological material obtained at autopsy or cardiac surgery (valve tissue, vegetations, embolic fragments or intracardiac abscess content)

**Major criteria:****1) Positive blood cultures:**

- It should be at least **3 sets blood culture samples from 3 different sites**: they are **positive** in **75%** of cases of **bacterial** endocarditis.
- Because bacteraemia may be periodic, blood cultures should not be taken simultaneously, but should be taken **sequentially from 3 different sites, 1 hour apart**.
- **Draw 3 samples of blood from 3 different sites with the first separated from the last by at least one hour over 24 hours**.
- **Two positive** blood cultures showing typical organisms consistent with infective endocarditis, such as *Streptococcus viridans* and the HACEK group, or
- Persistent bacteraemia from two blood cultures taken > 12 hours apart or three or more positive blood cultures where the pathogen is less specific such as *Staph aureus* and *Staph epidermidis*, or
- Positive serology for *Coxiella burnetii*, *Bartonella* species or *Chlamydia psittaci*, or
- Positive molecular assays for specific gene targets

**1) Evidence of endocardial involvement:**

- Positive echocardiogram: oscillating structures, abscess formation, new valvular regurgitation or dehiscence of prosthetic valves.

It is also important to remember that a normal echocardiogram **does not** exclude infective endocarditis.

**Minor criteria:**

- 1) Predisposing heart condition or intravenous drug use.
- 2) Microbiological evidence does not meet major criteria.
- 3) Fever > 38°C.
- 4) Vascular phenomena: major emboli, splenomegaly, clubbing, splinter haemorrhages, petechiae or purpura.
- 5) Immunological phenomena: glomerulonephritis, Osler's nodes, Roth spots, Janeway lesions.

## Infective endocarditis: prognosis and management

### Poor prognostic factors:

- 1) **Staph aureus** infection **acute** endocarditis (see below).
- 2) **I.V** drug abuse (often left and right sided disease).
- 3) Infection of the **aortic** rather than mitral valve.
- 4) **Prosthetic** valve endocarditis (esp 'early', acquired during surgery).
- 5) **Culture negative** endocarditis.
- 6) **Low complement** levels.
- 7) **Old age**.
- 8) **IDDM**.
- 9) Severe co-morbidities

Other factors that are crucial in prognostic assessment are:

- Endocarditis due to **fungus** or Gram **negative bacilli**.
- Endocarditis **complications** including heart failure, renal failure, stroke, septic shock and periannular complications, and
- **Echocardiographic** findings including severe left sided valve regurgitation, low LV EF%, pulmonary hypertension, large vegetations and severe prosthetic valve dysfunction.

**NB:** Infective endocarditis >>> streptococcal infection (Subacute bacterial endocarditis (*Streptococcus viridans*) >>> carries a good prognosis.

### Mortality according to organism:

- staphylococci - 30%
- bowel organisms - 15%
- streptococci - 5%

**Current antibiotic guidelines** (source: British National Formulary)

Scenario	Suggested antibiotic therapy
Initial blind therapy	<p><u>Native valve:</u></p> <ul style="list-style-type: none"> <li>• <u>Amoxicillin</u>, consider adding low-dose <u>gentamicin</u></li> </ul> <p>If penicillin allergic, <u>MRSA</u> or <u>severe sepsis:</u></p> <ul style="list-style-type: none"> <li>• <u>vancomycin</u> + low-dose <u>gentamicin</u></li> </ul>

Scenario	Suggested antibiotic therapy
	If prosthetic valve: <ul style="list-style-type: none"> <li><u>Vancomycin + rifampicin + low-dose gentamicin.</u></li> </ul>
Native valve endocarditis caused by staphylococci	<u>Flucloxacillin + gentamicin</u> If penicillin allergic or MRSA: <ul style="list-style-type: none"> <li>Vancomycin + gentamicin.</li> </ul>
Prosthetic valve endocarditis caused by staphylococci	Flucloxacillin + Rifampicin + low-dose gentamicin If penicillin allergic or MRSA: <ul style="list-style-type: none"> <li>Vancomycin + Rifampicin + low-dose gentamicin.</li> </ul>
<u>Endocarditis caused by fully-sensitive streptococci (e.g. viridans)</u>	<u>Benzylpenicillin.</u> If penicillin allergic: <ul style="list-style-type: none"> <li>Vancomycin + low-dose gentamicin</li> </ul>
Endocarditis caused by less sensitive streptococci	Benzylpenicillin + low-dose gentamicin If penicillin allergic: <ul style="list-style-type: none"> <li>Vancomycin + low-dose gentamicin</li> </ul>

The most useful laboratory test for monitoring the response to IEC treatment (which is usually obvious clinically) is **serial CRP estimation**. This is of much more use than the ESR, which is much slower to fall.

IEC caused by **candida albicans** over a **bicuspid aortic valve** in **IV drug abuser** patient >>> **Aortic valve replacement followed by Amphotericin B IV for 6 wks.**

**In Intravenous drug abuser (IVDA) a MRSA is the causative organism in about 60-70% of cases with haematogenous spread of bacteria resulting in frontal lobe abscess >>> IV flucloxacillin + gentamicin is the combination of choice till the result of culture.**

If MRSA is confirmed >>> IV vancomycin + gentamicin.

**Teicoplanin** has a similar spectrum of antimicrobial activity to vancomycin, but has slightly more anti-streptococcal activity than vancomycin and slightly less anti-staphylococcal activity. It is **not** a first line agent in the ttt of endocarditis.

**EX:** A young male patient after **RTA** and ORIF of # at left tibia and fibula, then after 1 wk. develops fever (38.5°C), tachycardia (130 bpm), low BP (100/60 mmHg), splinter haemorrhage on finger nails, systolic murmur, rise serum creatinine, urine: blood+, protein +, leucocytes+ >>> ? **IEC** due to **staph** due to his **extensive trauma** >>> **initial** blind ttt before results of blood culture is >>> **IV flucloxacillin + IV gentamicin**.

**Indications for surgery:**

- 1) Severe valvular incompetence.
- 2) Severe mitral regurgitation causing refractory pulmonary oedema.
- 3) Severe mitral regurgitation with signs of pulmonary hypertension.
- 4) Cardiac failure, as a result of valve destruction, refractory to standard medical treatment.
- 5) Aortic abscess (often indicated by a lengthening PR interval).
- 6) Infections resistant to antibiotics such as fungi infections or multi resistant organisms, brucella, coxiella, pseudomonas aeruginosa, vancomycin-resistant enterocoli.
- 7) Persistent bacteraemia despite appropriate antibiotic therapy.
- 8) Extension of infection to an extravalvular site.
- 9) Recurrent emboli after antibiotic therapy
- 10) Early prosthetic valve endocarditis (within 2 months).
- 11) Dehiscence or obstruction of a prosthetic valve.
- 12) Persistent fever for 10 days in culture-negative prosthetic valve endocarditis.

Valve surgery may be deferred until the patient is afebrile unless there is haemodynamic compromise, larger vegetations are seen or an abscess present.

The **ESC** European Society of Cardiology makes the following recommendations with regard to infective endocarditis related to cardiac devices:

- **Prolonged antibiotic therapy** and **device removal** are recommended.
- Percutaneous extraction is recommended in most patients with cardiac devices even those with large (>10 mm) vegetations.
- After device extraction, **reassessment** of the need for re-implantation is recommended, and
- Routine **antibiotic** prophylaxis is recommended before device implantation.

### **Infective endocarditis: prophylaxis**

The 2008 NICE guidelines have fundamentally changed the approach to infective endocarditis prophylaxis. What is not yet clear is if there are any circumstances in which NICE would recommend using antibiotic prophylaxis.

The 2008 guidelines from NICE have radically changed the list of procedures for which antibiotic prophylaxis is recommended.

NICE recommends the following procedures do **not** require prophylaxis:

- Dental procedures.
- Upper and lower gastrointestinal tract procedures
- Genitourinary tract; this includes urological, gynaecological and obstetric procedures and childbirth.
- Upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy.

The guidelines do however suggest:

- Any episodes of infection in people at risk of infective endocarditis should be investigated and treated promptly to reduce the risk of endocarditis developing.
- If a person at risk of infective endocarditis is receiving antimicrobial therapy because they are undergoing a gastrointestinal or genitourinary **procedure at a site where there is a suspected infection** they should be given an antibiotic that covers organisms that cause infective endocarditis

According to NICE guidelines, antibiotic [Prophylaxis against infective endocarditis \(CG64\)](#) is **not recommended in common cardiac valve abnormalities**.

**Prophylaxis is only recommended in those patients who are at highest risk of adverse outcomes on the development of endocarditis.** These patient groups include:



- 1) **Previous endocarditis.**
- 2) **Acquired valvular heart disease with stenosis or regurgitation.**
- 3) **HOCM.**
- 4) **Prosthetic** cardiac valve or prosthetic material used for cardiac valve repair.
- 5) **Unrepaired congenital cyanotic heart disease** including palliative shunts and conduits.
- 6) **Completely repaired congenital heart defect** with **prosthetic** material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure.
- 7) **Repaired congenital** heart disease with **residual defects** (persisting leaks or abnormal flow) at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialisation).
- 8) **Cardiac transplantation recipients** who develop cardiac **valve** abnormalities.

### Congenital heart disease: types

#### Acyanotic - most common causes

- 1) Ventricular septal defects (**VSD**) - **most common**, accounts for **30%**
- 2) Atrial septal defect (**ASD**): 10%
- 3) Patent ductus arteriosus (PDA)
- 4) Coarctation of the aorta

**VSDs** are more common than **ASDs**. However, in adult patients **ASDs** are the more common new diagnosis as they generally presents later.

#### Cyanotic - most common causes:

- 1) Tetralogy of Fallot (**F4**)
- 2) Transposition of the great arteries (**TGA**)
- 3) Tricuspid atresia (NOT mitral atresia)
- 4) Pulmonary valve stenosis
- 5) Total anomalous pulmonary venous connection (**TAPVC**): consists of an abnormality of blood flow in which all four pulmonary veins drain into systemic veins or the right atrium with or without pulmonary venous obstruction i.e. systemic and pulmonary venous blood mix in the RA.

Fallot's is more common than **TGA**. However, at birth **TGA** is the more common lesion as patients with Fallot's generally presenting at around 1-2 months following the identification of a murmur or cyanosis.

**TGA** is the most common presenting cause of cyanotic congenital heart disease.

**Congenital heart disease:**

- **Acyanotic:** VSD most common cause
- **Cyanotic:** TGA most common at birth, Fallot's most common overall

**N.B:**

- **Aortic regurgitation** may be a feature of **osteogenesis imperfecta**.
- The majority of cases of **neonates** with **complete heart block** (? neonatal lupus) may be caused by **autoimmune** disease, particularly **anti-Ro antibodies** in the **mother who has SLE during the pregnancy**.
- **Left ventricle (LV) hypoplasia** occurs when the **left** sided chambers **fail to develop** and blood enters the systemic circulation from the right ventricle via the pulmonary artery and a patent ductus arteriosus.

**Patent ductus arteriosus (PDA)**

Overview:

- Acyanotic congenital heart defect
- Connection between the pulmonary trunk and descending aorta
- More common in premature babies, born at high altitude or maternal rubella infection in the first trimester

Features:

- Left subclavicular thrill.
- **Continuous 'machinery'** murmur. But when the shunt **reverses** (as in patients with a large PDA and/or pulmonary disease) the murmur becomes **softer** and **shorter**.
- Large volume, bounding, collapsing pulse.
- Wide pulse pressure.
- Heaving apex beat.

Management:

- Indomethacin closes the connection in the majority of cases.
- If associated with another congenital heart defect amenable to surgery then prostaglandin E1 is useful to keep the duct open until after surgical repair.

### **Ventricular septal defects (VSD)**

Ventricular septal defects are the most common cause of congenital acyanotic heart disease. They close spontaneously in around **50%** of cases.

Non-congenital causes include post myocardial infarction.

Features:

- Classically a pan-systolic murmur which is louder in smaller defects

Complications:

- Right heart failure
- Eisenmenger's complex
- Infective endocarditis
- Aortic regurgitation: It is due to a poorly supported right coronary cusp resulting in cusp prolapse

### **Atrial septal defects (ASD)**

ASD is often first diagnosed in adulthood and represents **30% of all adult** congenital heart disease.

**Female:** male ratio is **3:1** and **75%** of them are ASD **ostium secundum**.

Communications at the level of the atria allows left-to-right shunting of blood, leading to considerable increase in right-heart output >> lead to **pulmonary hypertension**.

**Fixed splitting of S2** on auscultation and **mild systolic murmur** over P area.

ECG >>> **RBBB** ± Rt axis deviation

Patients often present with **AF**.

CXR >>> **pulmonary plethora**

Significant ASD should be repaired below the age of 10 years or as soon as possible if diagnosed in adulthood.

**TEE** can give sufficient anatomical data about the site and size of the defect.

It is well worth that patients undergoing **EPS** prior to any closure procedure.

Any abnormal pathways predisposing to atrial flutter/fibrillation should be considered for **RFA** radiofrequency ablation which can be curative.

**NB:** Atrial fibrillation is associated more with atrial septal defects

**NB:** In the **presence** of **Eisenmenger's syndrome**, the **maternal mortality** is approximately **40%** and **pregnancy is contraindicated**, with **older** maternal age increasing the risk of **pulmonary hypertension** and **Eisenmenger's**.

In the **absence** of any structural heart disease or Eisenmenger's, the pregnant woman with ASD has **no** significant increase in risk compared to the general population.

**Lutembacher's syndrome (= MS+ ASD± AF):**

This was first described in 1916 by Lutembacher, and is a syndrome characterised by both mitral stenosis and atrial septal defect (ASD). Both conditions may be congenital and occur concurrently, or the mitral stenosis may occur as a result of rheumatic fever or other cause. Incidence of Lutembacher's syndrome is higher in women due to the higher incidence of congenital ASD. Cardiac signs are mixed due to the two concurrent lesions. Presentation is typically in later life, with fatigue or atrial fibrillation. Ideally, surgery should be performed as early as possible due to the risks of Eisenmenger's syndrome in untreated patients.

Atrial Septal Defects make up 30% of congenital heart disease detected in the adult population. The female:male ratio is 2:1 and 75% of them are ostia secunda. They commonly present during pregnancy with either breathlessness or palpitations. There usually is no audible murmur with ASDs. The combination of right bundle branch block (RBBB) and right axis deviation on the electrocardiogram (ECG) makes an ostium secundum ASD more likely. These patients should have urgent echocardiographic assessment to assess the state of the right heart and be followed up very closely as the prognosis is very poor if they develop Eisenmenger's syndrome; early surgical intervention after the birth of the child is a consideration.

**EX:** Pregnant female + Palpitation + Incomplete RBBB + fixed S2 splitting > **Ostium secundum ASD >>> Urgent Echo and urgent surgical intervention after delivery.**

**Patent foramen ovale (PFO)**

Patent foramen ovale (PFO) is present in around 20% of the population.

It may allow embolus (e.g. from DVT) to pass from right side of the heart to the left side leading to a stroke - '**a paradoxical embolus**'.

Whilst atrial septal defects may allow emboli to pass from the right side of the heart to the left side, but the most common cause is a patent foramen ovale. There also appears to be an association between migraine and PFO. Some studies have reported improvement in migraine symptoms following closure of the PFO.

**Transoesophageal echocardiography (TOE)** is the investigation of choice to investigate for a PFO, although transthoracic echocardiography with contrast may be an alternative.

**Paradoxical embolisation**

For a right-sided thrombus (e.g. DVT) to cause a left-sided embolism (e.g. stroke) it must obviously pass from the right-to-left side of the heart.

The following cardiac lesions may cause such events:

- **Patent foramen ovale (PFO)** - present in around 20% of the population.
- Atrial septal defect (ASD) - a much less common cause.

**Transoesophageal echocardiography (TEE)** provides superior views of the atrial septum and therefore is preferred to transthoracic echocardiography for detecting patent foramen ovale.

<p><b><u>NB:</u></b> EX. a 24-year-old female develops transient slurred speech following a flight from Australia to the United Kingdom. Both a CT head and ECG are normal. Which one of the following tests is most likely to reveal the underlying cause?</p>
---

<p>A: Paradoxical embolus &gt;&gt;&gt; PFO most common cause &gt;&gt;&gt; do TEE.</p>
---

### **Eisenmenger's syndrome**

Eisenmenger's syndrome describes the reversal of a left-to-right shunt in a congenital heart defect due to pulmonary hypertension.

This occurs when an uncorrected left-to-right leads to remodelling of the pulmonary microvasculature, eventually causing obstruction to pulmonary blood and pulmonary hypertension.

The original murmur may disappear once Eisenmenger's syndrome develops.

Associated with:

- 1) Ventricular septal defect.
- 2) Atrial septal defect.
- 3) Patent ductus arteriosus.

Features:

- Original murmur may disappear
- Cyanosis
- Clubbing
- Right ventricular failure
- Haemoptysis, embolism

Management:

- Heart-lung transplantation is required

**NB:** Although patients with tetralogy of Fallot have, by definition, a ventricular septal defect they do not go on to develop Eisenmenger's syndrome.

**NB:** The **reversed patent ductus arteriosus (PDA)** >>> There is a **right-left shunt** from the pulmonary artery to the aorta just **distal** to the **left subclavian artery** >>> Pt 25 yrs. with **cyanosis of the lower limbs and clubbing of the toes but not the fingers.**

### Tetralogy of Fallot (TOF)

TOF is the most common cause of cyanotic congenital heart disease.

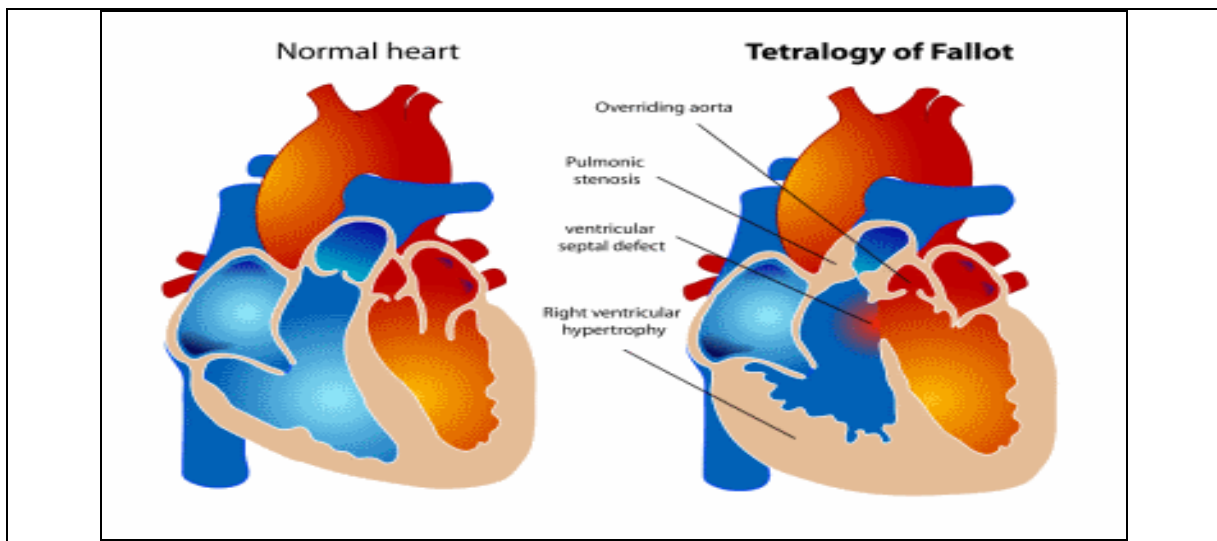
It typically presents at around 1-2 months, although may not be picked up until the baby is 6 months old.

However, at birth the transposition of the great arteries (TGA) is the more common lesion as patients with TOF generally present at around 1-2 months

TOF is a result of anterior mal-alignment of the **aortico-pulmonary septum**.

The **four** characteristic features are:

- 1) Ventricular septal defect (VSD)
- 2) Right ventricular hypertrophy
- 3) Right ventricular outflow tract obstruction, pulmonary stenosis
- 4) Overriding aorta



The severity of the right ventricular outflow tract obstruction determines the degree of cyanosis and clinical severity.

Other features:

- **Cyanosis**
- Causes a **right-to-left shunt**
- Ejection systolic murmur due to pulmonary stenosis (the VSD doesn't usually cause a murmur).
- A right-sided aortic arch is seen in 25% of patients
- CXR shows a 'boot-shaped' heart.
- ECG shows right ventricular hypertrophy.

Management:

- Surgical repair is often undertaken in two parts.
- A Blalock shunt (anastomosis of subclavian artery to pulmonary artery) it leads to a weak left radial pulse.
- Cyanotic episodes may be helped by beta-blockers to reduce infundibular spasm.

**NB:** ASD, VSD and PDA >>> Lt to RT Shunt,

But, TOF >>>> RT to Lt Shunt.

### **Ebstein's anomaly**

It is a **rare** condition probably accounting for around **0.5%** of cases of congenital heart disease.

Ebstein's anomaly is a congenital heart defect characterised by **low insertion of the tricuspid valve** (displacement of the tricuspid valve towards the apex) resulting in a large atrium and small ventricle.

It is sometimes referred to as '**atrialisation**' of the **right ventricle** and **hypoplastic RV** and an associated defects such as ASD.

Associations:

- 1) **Tricuspid regurgitation** (**pan-systolic** murmur, **giant V waves** in JVP).
- 2) **WPWS**: occurs in around 15% of the patients.
- 3) **RBBB**

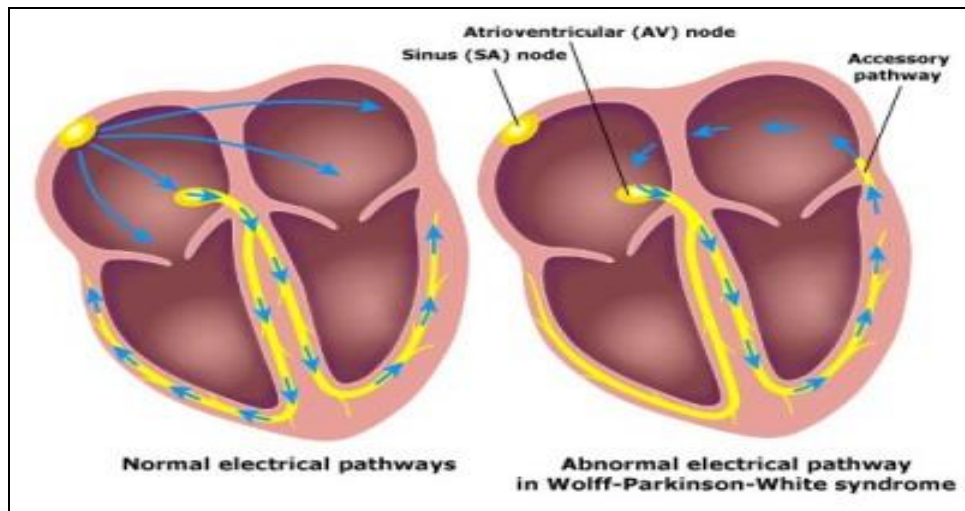
Ebstein's anomaly may be caused by exposure to **lithium** ( $\text{LiCO}_3$ ) **in-utero**.

### **Wolff-Parkinson White syndrome (WPWS)**

It is caused by a congenital accessory conducting pathway between the atria and ventricles leading to an atrioventricular re-entry tachycardia (AVRT).

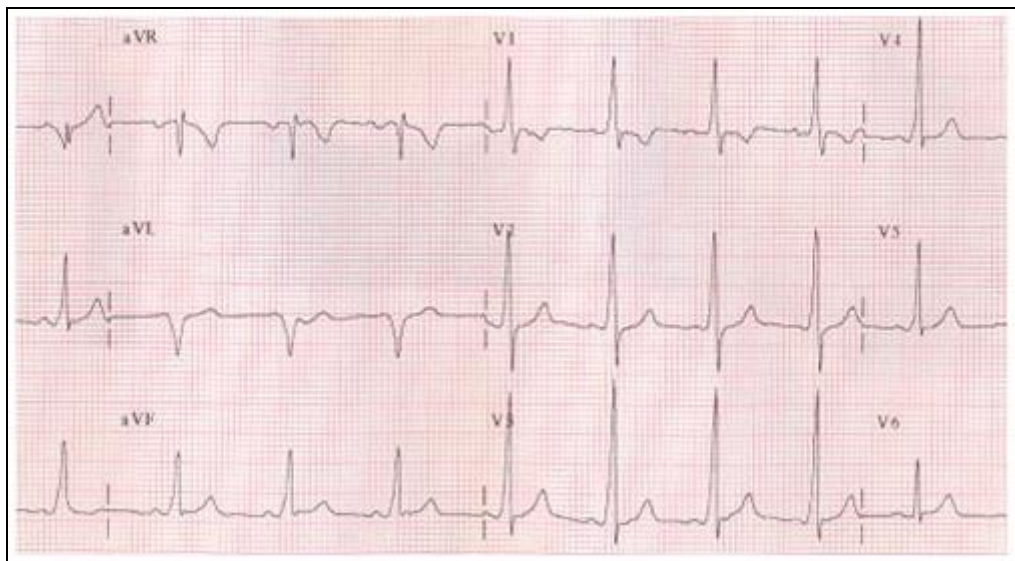
As the accessory pathway does not slow conduction AF can degenerate rapidly to VF.



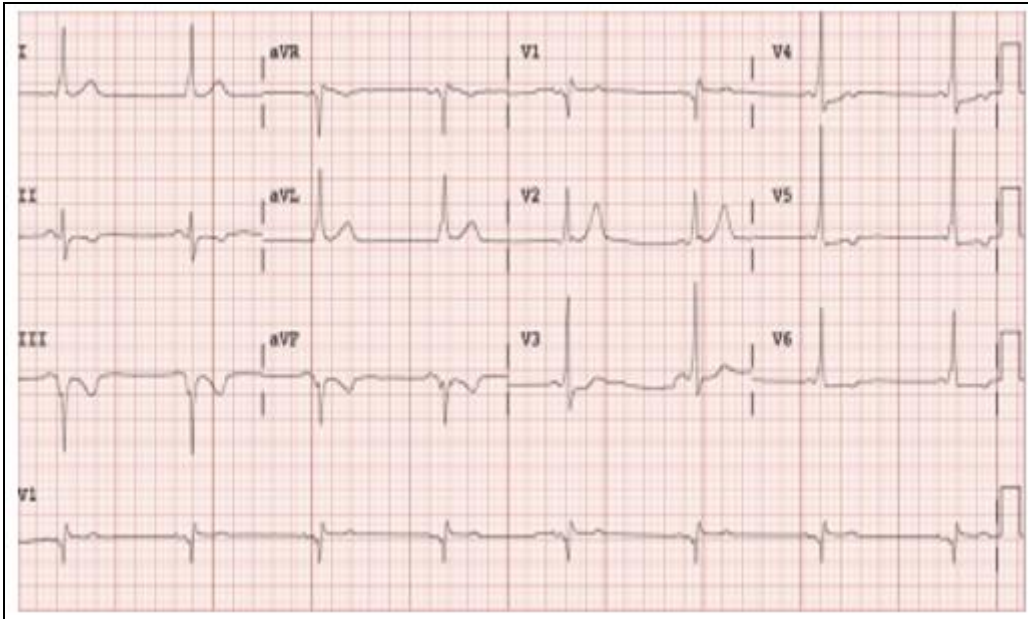


Possible ECG features include:

- **Short PR interval**
- **Wide QRS complexes** with a **slurred upstroke** - 'delta wave'
- Right axis deviation if left-sided accessory pathway\*
- Left axis deviation if right-sided accessory pathway\*



WPWS: Type **A**: **dominant R** wave in **V1**, **left-sided** pathway, and **Right** axis deviation:



WPWS: Type **B**: no dominant R wave in V1, right-sided pathway, left axis deviation.

Note the non-specific ST-T changes which are common in WPW and may be mistaken for ischaemia.

Differentiating between type A and type B

- Type **A** (left-sided pathway): **dominant R wave in V1**
- Type **B** (right-sided pathway): no dominant R wave in V1

Associations of WPW: **(5)**:

- 1) HOCM
- 2) Mitral valve prolapse (MVP)
- 3) Ebstein's anomaly
- 4) Thyrotoxicosis
- 5) Secundum ASD

Management

- **Definitive** treatment >>> **EPS** with **radiofrequency ablation (RFA)** of the **accessory** pathway.
- **Medical** therapy: **Flecainide**, Amiodarone, Atenolol, Sotalol.

If **not symptomatic** (no palpitations or headedness) >>> so **reassurance**.

Anticoagulation is not indicated.

Risk of arrhythmia after ablation is of the order of 7% over 5 years.

In the majority of cases, or in a question without qualification, Wolff-Parkinson-White syndrome is associated with left axis deviation.

NB: Sotalol should be avoided if there is coexistent atrial fibrillation as prolonging the refractory period at the AV node may increase the rate of transmission through the accessory pathway, increasing the ventricular rate and potentially deteriorating into ventricular fibrillation.

NB: Adenosine should be avoided as blocking the AV node can paradoxically increase ventricular rate resulting in fall in cardiac output.

NB: Verapamil and digoxin should also be avoided in patients with Wolff-Parkinson White as they may precipitate VT or VF.

**NB: D.D Tall R in V1:**

- WPWS type A,
- RBBB,
- Posterior MI,
- Dressler's syndrome post MI and
- Dextrocardia.

### Hypertension: diagnosis and management

NICE published updated guidelines for the management of hypertension.

- Classifying hypertension into stages.
- Recommending the use of **ambulatory blood pressure monitoring (ABPM)** and home blood pressure monitoring (HBPM).
- In the past there was overtreatment of '**white coat**' hypertension. The use of ambulatory blood pressure monitoring (ABPM) aims to reduce this. There is also good evidence that ABPM is a better predictor of cardiovascular risk than clinic blood pressure readings.
- Calcium channel blockers are now considered superior to thiazides.
- Bendroflumethiazide is no longer the thiazide of choice.

### **Blood pressure classification:**

This becomes relevant later in some of the management decisions that NICE advocate.

Stage	Criteria
<b>Stage 1 hypertension</b>	Clinic BP $\geq 140/90$ mmHg and subsequent ABPM daytime average or HBPM average BP $\geq 135/85$ mmHg
<b>Stage 2 hypertension</b>	Clinic BP $\geq 160/100$ mmHg and subsequent ABPM daytime average or HBPM average BP $\geq 150/95$ mmHg
<b>Severe hypertension</b>	Clinic systolic BP $\geq 180$ mmHg, or clinic diastolic BP $\geq 110$ mmHg

### Diagnosing hypertension:

If a BP reading is  $\geq 140 / 90$  mmHg patients should be offered ABPM to confirm the diagnosis.

Patients with a BP reading of  $\geq 180/110$  mmHg should be considered for immediate treatment.

Ambulatory blood pressure monitoring (ABPM):

- At least 2 measurements per hour during the person's usual waking hours (for example, between 08:00 and 22:00).
- Use the average value of at least 14 measurements.

If ABPM is not tolerated or declined HBPM should be offered.

Home blood pressure monitoring (HBPM):

- For each BP recording, two consecutive measurements need to be taken, at least 1 minute apart and with the person seated.
- BP should be recorded twice daily, ideally in the morning and evening.
- BP should be recorded for at least 4 days, ideally for 7 days.
- Discard the measurements taken on the first day and use the average value of all the remaining measurements.

### Managing hypertension:

Lifestyle advice should not be forgotten and is frequently tested in exams:

- **Weight reduction** produce the **greatest** reduction in BP (a **10 kg** weight loss is expected to decrease the BP by **15-20 mmHg**).
- A low **salt** diet is recommended, aiming for less than 6g/day, ideally 3g/day. The average adult in the UK consumes around 8-12g/day of salt. A recent BMJ paper showed that lowering salt intake can have a significant effect on blood pressure. For example, reducing salt intake by 6g/day can lower systolic blood pressure by 10mmHg.

- **Caffeine** intake should be reduced.
- Stop **smoking**,
- Drink less **alcohol**,
- Eat a balanced diet rich in **fruit and vegetables**.

**ABPM/HBPM  $\geq$  135/85 mmHg (i.e. stage 1 hypertension):**

- Treat if  $< 80$  years of age AND any of the following apply; target organ damage, established cardiovascular disease, renal disease, diabetes or a 10-year cardiovascular risk equivalent to 20% or greater.

**ABPM/HBPM  $\geq$  150/95 mmHg (i.e. stage 2 hypertension):**

- Offer drug treatment regardless of age.

For patients  $< 40$  years consider referral to exclude secondary causes.

**Step 1 treatment:**

- Patients  $< 55$ -years-old: **ACE inhibitor** (A)
- Patients  $> 55$ -years-old **or** of Afro-Caribbean origin: **CCBs** (C)

**Step 2 treatment:**

- **ACE inhibitor + calcium channel blocker** (A + C)

**Step 3 treatment:**

- Add a **thiazide** diuretic (D, i.e. A + C + D)
- NICE now advocate using either chlorthalidone (12.5-25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide.

NICE define a clinic BP  $\geq 140/90$  mmHg after step 3 treatment with optimal or best tolerated doses as **resistant hypertension**. They suggest step 4 treatment or seeking expert advice.

**Step 4 treatment:**

- Consider further diuretic treatment.
- If potassium  $< 4.5$  mmol/l add spironolactone 25mg OD.
- If potassium  $> 4.5$  mmol/l add higher-dose thiazide-like diuretic ttt.
- If further diuretic therapy is not tolerated, or is contraindicated or ineffective, consider an alpha- or beta-blocker.
- If BP still not controlled seek specialist advice.

Although polypharmacy is in general to be avoided, in a patient with recognised HTN **adding in a second drug is more effective than increasing doses of a first drug.**

Those **under 55 yrs.** old with HTN are advised to start on an **ACE inhibitor** at first (or **ARB blocker** should they be intolerant).

The starting dose of **Ramipril** is **1.25 mg** rather than 10 mg, which is **up titrated** in the absence of hypotension depending on satisfactory renal function.

ACE inhibitors have reduced efficacy in **black** patients (**Afro-Caribbean origin**) they have lower renin levels and are therefore not used first-line, so you can use **CCB** e.g. **Amlodipine** but **if not tolerated** due to LL oedema, so can use **thiazide**, and if still high BP you can **use ARBs like Valsartan**.

**CCBs** are presently recommended as first-line treatment in those **over 55**, or all patients of **African or Caribbean descent**.

If a CCB is not suitable, for example because of oedema or intolerance, or if there is evidence of HF or a high risk of HF, offer a **thiazide**-like diuretic.

NB:  $\beta$ B is not recommended as a 1<sup>st</sup> or 2<sup>nd</sup> line anti-hypertensive agent, particularly in obese population because of its association with impaired glucose tolerance.

The NICE guidelines on HTN advise **against** using **beta-blockers** as **routine 'first line'** therapy for **uncomplicated** hypertension.

Review of several randomised controlled trials suggested that first line beta-blockers were not as good at decreasing mortality as other classes of antihypertensive drugs and were less well tolerated.

**Blood pressure targets:**

	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg



Recommendations for target blood pressure (BP) differ slightly among different guidelines. British Hypertension Society Guidelines for Hypertension Management (BHS-IV) recommend a goal BP of less than 130/80 mmHg for patients with diabetes, renal impairment and established cardiovascular disease; while a Joint Negotiating Committee (JNC) 7 report and American College of Cardiology/American Heart Association Guidelines recommend a target BP of less than 140/90 mmHg in non-diabetic patients with cardiovascular disease.

Goal BP **less than 130/85 mmHg** for patients with DM, CKD and established CVD like IHD. (BHS).

While in non-diabetic patients with CVD, the target BP is **less than 140/90 mmHg**. (JNC) and (ACC/AHA).

**New drugs: Direct renin inhibitors:** e.g. Aliskiren (branded as Rasilez).

- By inhibiting renin blocks the conversion of angiotensinogen to angiotensin I.
- No trials have looked at mortality data yet. Trials have only investigated fall in blood pressure. Initial trials suggest aliskiren reduces BP to a similar extent as ACEIs or ARBs.
- Adverse effects were uncommon in trials although diarrhoea was occasionally seen.
- Only current role would seem to be in patients who are intolerant of more established antihypertensive drugs.

**Isolated systolic hypertension (ISH):**

- ISH is common in the elderly, affecting around **50%** of people **older than 70 years old**.
- ISH (systolic BP **>160** and diastolic BP **<90** mmHg).
- It is associated with a **greater risk than combined** systolic/diastolic hypertension.
- The Systolic Hypertension in the Elderly Program (SHEP) back in 1991 established that treating ISH reduced both strokes and IHDs.
- The NICE guidelines recommended treating isolated systolic hypertension **the same way as standard hypertension**. (Previously thiazides were recommended as first line agents).

## Malignant hypertension

Basics:

- Severe hypertension (e.g.  $\geq 200/130$  mmHg).
- Occurs in both essential and secondary types.
- Fibrinoid necrosis of blood vessels, leading to retinal haemorrhages, exudates, and proteinuria, haematuria due to renal damage (benign nephrosclerosis).
- Can lead to cerebral oedema → encephalopathy.

Features:

- Classically: severe headaches, nausea/vomiting, visual disturbance
- However chest pain and dyspnoea common presenting symptoms
- Papilledema
- Severe: encephalopathy (e.g. seizures)

Management:

- Reduce diastolic but no lower than 100mmHg within 12-24 hrs
- Bed rest
- Most patients: oral therapy e.g. atenolol
- If severe/encephalopathy: IV sodium nitroprusside / labetalol

According to NICE guidelines, you should **refer patients to specialist care** the same day if they have:

- **Accelerated hypertension** (BP usually higher than **180/110** mmHg with signs of **papilledema** and/or **retinal haemorrhage**), or
- **Suspected pheochromocytoma** (labile or postural hypotension, headache, palpitations, pallor and diaphoresis).

## Centrally acting antihypertensives:

Examples of centrally acting antihypertensives include:

- 1) **Methyldopa**: used in the management of hypertension during pregnancy.
- 2) **Clonidine**: the antihypertensive effect is mediated through stimulating alpha-2 adrenoceptors in the vasomotor centre.
- 3) **Moxonidine (Physiotense ® 0.2 mg tab)**: used in the management of essential hypertension when conventional antihypertensive have failed to control blood pressure.



### Na Nitroprusside

- It is a potent short acting vasodilator, which acts via the nitric oxide pathway to increase **cGMP** within smooth muscle cells.
- It has a rapid hypotensive effect that begins to appear **within 30-60 seconds** of commencing the infusion.
- It is **light sensitive** and degrades to cyanide if exposed to sunlight; as such it is delivered from a covered infusion bag.
- SE: nausea, sweating, headache and twitching.
- Overdose may be associated with accumulation of **cyanide**.
- Cobalamin plays a role in cyanide metabolism and B12 levels tend to fall as cyanide level rise.
- Na nitroprusside use is not recommended in **B12 deficiency** states.
- Indications:
  - HTN emergency.
  - Dissecting aortic aneurysm
  - Acute cardiac failure
  - Acute VSD
  - Acute MR
- Contraindications:
  - Vit B12 deficiency
  - Severe liver disease
  - Leber's optic atrophy

**EX:** Pt at ICU has severe hypertension on **Na Nitroprusside** and he is stable, after a few hours later he, just after the **nursing shift change**, he has become acutely confused, SOB, central chest pain, abdominal pain, vomiting, BP 100/60 mmHg, PH 7.1, metabolic acidosis, widespread ST depression consistent with myocardial ischaemia >>> **Cyanide poisoning** may be due to uncover of Na Nitroprusside so **it degrades in sunlight to form cyanide** >>> TTT: **Dicobalt edetate** 300 mg IV bolus and can be repeated 3 times, **Nitrate** is an alternative potential for cyanide poisoning if edetate is unavailable.

### Diabetes mellitus: hypertension management

Hypertension is an added cardiovascular risk factor for diabetics and should therefore be actively looked for and treated.

It is also a risk factor for the development of diabetic nephropathy.

Selected points:

- The blood pressure target for diabetics is 140/80 mmHg, but.
- If there is end-organ damage the target is 130/80 mmHg.

- ACEIs are first-line regardless of age.
- Otherwise managed according to standard NICE guidelines.
- Avoid the routine use of beta-blockers in uncomplicated hypertension, particularly when given in combination with thiazides, as they may cause insulin resistance, impair insulin secretion and alter the autonomic response to hypoglycaemia.

**NB:** The use of beta-blockers in treating hypertension has declined sharply in the past 5 years. Why? >>> Due to they are less likely to prevent stroke + potential impairment of glucose tolerance.

### Angiotensin-converting enzyme inhibitors (ACEIs)

ACE inhibitors are now the established first-line treatment in younger patients with hypertension and are also extensively used to treat heart failure.

They are known to be **less** effective in ttt of HTN in **Afro-Caribbean** patients.

ACE inhibitors are also used to treat diabetic nephropathy and have a role in secondary prevention of ischaemic heart disease.

Mechanism of action:

- Inhibit the conversion angiotensin I to angiotensin II

Side-effects:

- Cough: occurs in around **15%** of patients and may occur up to a year after starting treatment. Thought to be due to increased **bradykinin** levels.
- Angioedema: may occur up to a year after starting treatment.
- Hyperkalaemia
- First-dose hypotension: more common in patients taking diuretics.

Cautions and contraindications:

- Pregnancy and breastfeeding - avoid
- Renovascular disease - significant renal impairment may occur in patients who have undiagnosed bilateral renal artery stenosis.
- Severe Aortic stenosis - may result in hypotension.
- HOCM
- Patients receiving high-dose diuretic therapy (more than 80 mg of furosemide a day) - significantly increases the risk of hypotension.
- Hereditary of idiopathic angioedema.

### Monitoring:

- Urea and electrolytes should be checked before treatment is initiated and after increasing the dose
- A rise in the creatinine and potassium may be expected after starting ACE inhibitors.

**Acceptable changes are an increase in serum creatinine, up to 30% from baseline, a decrease in eGFR of up to 25% and an increase in potassium up to 5.5 mmol/l.**

### Hypertension: secondary causes

**Renal** - accounts for **80%** of secondary hypertension:

- Glomerulonephritis
- Pyelonephritis
- Adult polycystic kidney disease
- Renal artery stenosis

### Endocrine disorders:

- Cushing's syndrome
- Conn's syndrome (Primary hyperaldosteronism)
- Liddle's syndrome
- Congenital adrenal hyperplasia (**11-beta hydroxylase deficiency**)
- Phaeochromocytoma
- Acromegaly

### Others:

- Coarctation of the aorta
- Pregnancy
- Combined oral contraceptive pill
- Steroids
- NSAIDs
- MAOI

### Coarctation of the aorta

Coarctation of the aorta describes a congenital narrowing of the descending aorta. The most common type of coarctation of the aorta seen in adults is the postductal variety, i.e. the aortic narrowing is distal to the ductus arteriosus.

This means that the **upper limb** BP is **greater** than that in the lower limbs as the narrowing occurs after the left subclavian artery branches from the aorta.

Overview:

- More common in males (despite association with Turner's syndrome)

Features:

- Infancy: heart failure
- Adult: hypertension
- **Radio-femoral delay**
- Mid **systolic** murmur, **maximal over back (thoracic spines)**
- Apical click from the aortic valve
- **Notching of the inferior border of the ribs** (due to collateral vessels) is not seen in young children (**scalloping of the posterior ribs on CXR**).

Associations: (4)

- 1) Turner's syndrome.
- 2) Bicuspid aortic valve.
- 3) Berry aneurysms.
- 4) Neurofibromatosis.

### Heart failure: NYHA classification (The New York Heart Association)

NYHA classification 1928 is widely used to classify the severity of heart failure:

#### NYHA Class I:

- No symptoms
- No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations

#### NYHA Class II:

- Mild symptoms
- Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations or dyspnoea

#### NYHA Class III:

- Moderate symptoms
- Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms

**NYHA Class IV:**

- Severe symptoms
- Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity

**Heart failure: diagnosis**

NICE issued updated guidelines on diagnosis and management in 2010.

The choice of investigation is determined by whether the patient has previously had a myocardial infarction (MI) or not.

Previous MI >>>> arrange **echocardiogram** within 2 weeks.

No previous MI >>>> measure serum natriuretic peptides (**BNP**):

- If levels are 'high' arrange echocardiogram within 2 weeks
- If levels are 'raised' arrange echocardiogram within 6 weeks

**B-type natriuretic peptide (BNP)**

B-type natriuretic peptide (BNP) is a hormone produced mainly by the **left ventricular** myocardium in response to strain (volume overload).

Whilst heart failure is the most obvious cause of raised BNP levels any cause of left ventricular dysfunction such as myocardial ischaemia or valvular disease may raise levels.

Raised levels may also be seen due to reduced excretion in patients with chronic kidney disease.

Factors which reduce BNP levels include treatment with ACEIs, ARBs and diuretics.

So, BNP has a good negative predictive value rather than positive predictive value (i.e. like D-Dimer in PE).

Effects of BNP:

- 1) Vasodilator
- 2) ↑ GFR and inhibit Na reabsorption >>> Diuretic and natriuretic
- 3) Suppresses both sympathetic tone and the renin-angiotensin-aldosterone system.

**Clinical uses of BNP:**

**Diagnosing patients with acute dyspnoea:**

- A low concentration of BNP (< 100 pg/ml) makes a diagnosis of heart failure unlikely, but raised levels should prompt further investigation to confirm the diagnosis.
- NICE currently recommends BNP as a helpful test to rule out a diagnosis of heart failure.

**Prognosis in patients with chronic heart failure:**

- Initial evidence suggests **BNP is an extremely useful marker of prognosis**

**Guiding treatment in patients with chronic heart failure:**

- Effective treatment lowers BNP levels

**Screening for cardiac dysfunction:**

- **Not** currently recommended for population screening.

	<b>BNP</b>	<b>NTproBNP</b>
<b>High levels</b>	> 400 pg/ml (116 pmol/litre)	> 2000 pg/ml (236 pmol/litre)
<b>Raised levels</b>	100-400 pg/ml (29-116 pmol/litre)	400-2000 pg/ml (47-236 pmol/litre)
<b>Normal levels</b>	<u>&lt; 100 pg/ml</u> (29 pmol/litre)	< 400 pg/ml (47 pmol/litre)

**Factors which alter the BNP level:**

<b>Increase BNP levels</b>	<b>Decrease BNP levels</b>
Left ventricular hypertrophy Ischaemia Tachycardia Right ventricular overload Hypoxaemia (including PE) <u>GFR</u> < 60 ml/min	➤ <u>Obesity</u> ➤ <u>Diuretics</u> ➤ ACE inhibitors ➤ ARBs ➤ Beta-blockers ➤ Aldosterone

Increase BNP levels	Decrease BNP levels
Sepsis COPD Diabetes Age > 70 Liver cirrhosis	antagonists

### Atrial natriuretic peptide (ANP)

Basics:

- Secreted mainly from **myocytes** of right atrium and **ventricle** in response to increased blood volume.
- Secreted by both the right and left **atria** (**right** >> left)
- 28 amino acid peptide hormone, which acts via cGMP
- **Degraded by endopeptidases**

Actions:

- 1) Powerful **vasodilator**
- 2) **Natriuretic**, i.e. promotes excretion of sodium
- 3) Lowers BP
- 4) Antagonises actions of angiotensin II, aldosterone

### Heart failure: drug management

A number of drugs have been shown to improve mortality in patients with chronic heart failure:

- 1) **ACE inhibitors** (SAVE, SOLVD, CONSENSUS)
- 2) **Beta-blockers** (CIBIS)
- 3) **Spironolactone** (RALES)
- 4) **Hydralazine with nitrates** (VHEFT-1)

No long-term reduction in mortality has been demonstrated for loop diuretics such as furosemide.

NICE issued updated guidelines on management in 2010, key points include:

- First-line treatment for all patients is both a ACEIs and a beta-blocker.
- Second-line treatment is now either an aldosterone antagonist, angiotensin II receptor blocker or a hydralazine in combination with a nitrate.

- If symptoms persist cardiac resynchronisation therapy (CRT) or digoxin\* should be considered.
- Diuretics should be given for fluid overload.
- Offer annual influenza vaccine
- Offer one-off\*\* pneumococcal vaccine

NICE guidelines recommend the introduction of an ACE inhibitor prior to a beta-blocker in patients with chronic heart failure.

Both carvedilol and bisoprolol have been shown to reduce mortality in stable heart failure. The other beta-blockers have no evidence base to support their use.

The **β blockers should be discontinued** in **acute fluid overload**.

The RALES trial showed that spironolactone 25 mg daily reduced mortality by 30% when added to therapy of heart failure.

\*Digoxin has also not been proven to reduce mortality in patients with heart failure. It may however improve symptoms due to its inotropic properties. Digoxin is strongly indicated if there is coexistent atrial fibrillation.

\*\*Adults usually require just one dose but those with asplenia, splenic dysfunction or chronic kidney disease need a booster every 5 years

**EX:** A 62-year-old female is reviewed in the clinic despite current treatment with furosemide, bisoprolol, enalapril and spironolactone she remains breathless on minimal exertion and there is minimal ankle oedema, Echo: EF 35%. A combination of isosorbide dinitrate with hydralazine has been tried recently but had to be stopped due to side-effects. What additional medication would best help her symptoms? >>>  
**Digoxin / CRT.**

Digoxin may be useful in this situation whether the patient is in atrial fibrillation or not. Whilst it has not been shown to be of prognostic benefit it may help reduce symptoms. In the United States a large proportion of patients with heart failure take digoxin for this reason. Another option to consider in such a patient would be a CRT.

**CRT (Biventricular pacemaker implantation)** is recommended by NICE guidance for patients as long as they are currently experiencing or have recently experienced (NYHA) class III-IV symptoms:

- 1) They are in **sinus** rhythm with **wide QRS**:
  - a. Either with a QRS duration of 150 ms or longer estimated by standard (ECG).
  - b. Or with a QRS duration of 120-149 ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography.



- 2) They have a left ventricular ejection fraction **LVEF of 35%** or less.
- 3) They are receiving optimal **pharmacological** therapy.

**The following medications may exacerbate heart failure:**

- **Pioglitazone** is contraindicated as it causes fluid retention.
- **Verapamil**: negative inotropic effect.
- **NSAIDs/glucocorticoids**: used with caution as they cause fluid retention.
- Class I antiarrhythmics; **Flecainide** (negative inotropic and proarrhythmic effect). Flecainide is contraindicated in patients with structural heart disease and IHD.

There are a number of biochemical parameters which provide useful prognostic information.

**Prognostic markers include: (2 High & 2 low)**

- 1) **High BNP/NT-pro-BNP**
- 2) **↑ Uric acid.**
- 3) **Anaemia**
- 4) **Hyponatraemia**

**NB:** Non-iatrogenic hyponatraemia in CHF carries a poor prognosis. It was thought that specific vasopressin antagonist may offer a significant prognostic antagonist, but the data so far have proved very disappointing.

**NB:** Serum calcium is not a useful in prognosis in heart failure.

**Aortic dissection: management**

The typical history of aortic dissection is **sudden collapse** with **acute severe retrosternal central crushing chest pain within minutes** radiating to the **back** in the presence of **a recent normal exercise test (i.e. not IHD)** and may be with **history of chronic HTN**.

**Stanford classification**

- **Type A - ascending aorta, 2/3 of cases**
- **Type B - descending aorta, distal to left subclavian origin, 1/3 of cases**

**DeBakey classification**

- **Type I - originates in ascending aorta, propagates to at least the aortic arch and possibly beyond it distally**

- Type II - originates in and is confined to the ascending aorta
- Type III - originates in descending aorta, rarely extends proximally but will extend distally

**Associations (7):**

- 1) Hypertension
- 2) Trauma
- 3) Bicuspid aortic valve
- 4) Collagens: Marfan's syndrome, Ehlers-Danlos syndrome
- 5) Turner's and Noonan's syndrome
- 6) Pregnancy
- 7) Syphilis

**Complications of backward tear**

- 1) **Aortic regurgitation**
- 2) **Inferior MI**: pattern often seen due to right coronary involvement
- 3) **Cardiac tamponade**

**Complications of forward tear**

- Unequal arm pulses and BP
- Stroke
- Renal failure

**Type A**

- Surgical management, but BP should be controlled to a target systolic SBP of 100-120 mmHg by IV Labetalol, whilst awaiting intervention.

**Type B**

- Conservative management
- Bed rest
- Reduce blood pressure IV labetalol to prevent progression
- Endovascular repair of type B aortic dissection may have a role in the future

**Aortic dissection:**

- Type A - Ascending aorta - control BP (IV labetalol) + surgery.
- Type B - Descending aorta - control BP (IV labetalol).

**Beta blockers** are the main stay of medical therapy, as they are negative inotropic agent that will reduce the rate of left ventricular ejection and shear on the aortic wall.

The aim is to reduce **SBP to 100-120 mmHg** and the **HR to near 60 bpm**.

Na nitroprusside is a useful additional adjunct, it can be added if BP is not controlled by  $\beta$ B, but should **not** be used alone as it may increase rate of LV ejection.

Hydralazine should be avoided for the same reason.

If  $\beta$ B is unsuitable, then CCBs particularly non-dihydropyridines such as diltiazem would be a logical alternative.

Mortality for untreated aortic dissection is 25-30% at 24 hours and 65-70% at 2 weeks; dissections confined to the ascending aorta are associated with better survival (80%).

NB: Features that favour oesophageal rupture over aortic dissection include:

- The history of onset while eating
- Blood pressure equal in both arms
- No diastolic murmur
- Good peripheral pulses
- Presence of a pleural effusion.

### **Aortic stenosis**

- **Ejection systolic murmur** radiating to the carotid area and axilla.
- **Low Cardiac output symptoms** (chest pain, dyspnoea, syncope, episodes of pulmonary oedema etc.).
- AS may be asymptomatic.
- The classical symptoms are only in 30-40% of individuals with AS.
- When symptoms appear, survival without surgery is only average 2-3 years.
- SCD occurs in 1-2% of asymptomatic AS patients per year.

Features of severe aortic stenosis:

- Narrow pulse pressure
- Small volume pulse
- Slow rising pulse
- Delayed ESM
- Soft/absent S2
- In severe AS >>> reversed splitting of S2.
- S4

- Thrill
- Duration of murmur
- Left ventricular hypertrophy or failure >>> **Displaced apex beat** (The apex beat is not normally displaced in aortic stenosis. Displacement would indicate left ventricular dilatation and hence severe disease).
- An overestimation of the severity of aortic stenosis can occur due to large volumes of blood passing over the valve at high velocities, which occurs in aortic regurgitation.

Aortic stenosis is associated with a worse prognosis when accompanied by left ventricular **(LV) dysfunction**.

Although the severity of valvular calcification is prognostically important in an asymptomatic patient **the most important predictor is LV function**.

Causes of aortic stenosis:

- 1) **Degenerative** calcification (most common cause in older patients > 65 years).
- 2) **Bicuspid** aortic valve (most common cause in younger patients < 65 years).
- 3) Congenital: William's syndrome (supra-valvular aortic stenosis).
- 4) Post-rheumatic disease.
- 5) Subvalvular: HOCM.

Management:

- 1) If asymptomatic then observe the patient is general rule.
- 2) If symptomatic then valve replacement.
- 3) If asymptomatic but valvular gradient > 50 mmHg and with features such as left ventricular systolic dysfunction then consider surgery.
- 4) Balloon valvuloplasty is limited to patients with critical aortic stenosis who are not fit for valve replacement.
- 5) Endocarditis prophylaxis with antibiotics is no longer recommended.

AS >>> AVR if **symptomatic**, otherwise cut-off is gradient of 50 mmHg.

Usually before valve replacement >>>do **coronary angiography**

The patient's **symptomatology** is probably the most important determinant in terms of the decision to operate for AVR.

A gradient of 50 mmHg would be regarded as moderate to severe AS but if asymptomatic nothing would be done.

LVH is a common feature of AS and does not influence the decision for surgery.

Calcific aortic disease is not of itself important and the gradient should be considered.

**NB:** Left ventricular systolic dysfunction/ failure >>> will result in a decreased flow-rate across the aortic valve and hence a quieter murmur of AS.

**NB:** ACEI is contraindicated in severe Aortic stenosis.

**NB:**

If patient has severe left ventricular (LV) dysfunction, and calculated valve area in such patients can be falsely low because low cardiac output reduces the valve opening forces. It is important to distinguish patients with true severe aortic stenosis (AS) with secondary LV dysfunction from those who have a falsely low calculated aortic valve area because of low cardiac output. An important method of distinguishing between the two conditions is to assess the haemodynamics after increasing the cardiac output by dobutamine infusion during echocardiography or cardiac catheterisation. Patients with truly severe AS manifest an increase in transaortic pressure gradient while the valve surface area remains the same during dobutamine infusion; while those with falsely low calculated valve area manifest an increase in calculated valve surface area. Dobutamine echocardiography is also important to assess LV contractile reserve. Patients who have 20% or more increase in stroke volume after dobutamine infusion have a much better prognosis after surgery compared to those who do not have LV contractile reserve.

**NB:** Symptomatic AS+ small aortic valve area+ small PG (less than 50 mmHg) + low EF% >>> should repeat Echocardiography with dobutamine infusion

**EX:** Pt with severe AS for AVR and also had LAD stenosis by 80% as revealed by coronary angiography >>> so management is AVR PLUS bypass grafting of the LAD using the left internal mammary artery (LIMA).

This patient has severe symptomatic aortic stenosis, which is an indication for aortic valve replacement. He also has LAD stenosis. As the patient is to have AVR, a concomitant bypass grafting of the LAD using the LIMA is the most appropriate option. The long-term patency of the LIMA is superior to that of a saphenous vein graft.

Percutaneous balloon aortic valvotomy is only used as a bridge to surgery in selected patients who are too sick to undergo AVR.

**Heyde's syndrome:** الحاجة هايدى

It is a well-known association between **microcytic anaemia** and **calcific aortic stenosis**.

Mechanism: destruction of vWF as the platelets traverse the stenosed valve resulting in bleeding per rectum.

TTT: **Aortic valve replacement**,

The investigation of choice after valve replacement is the mesenteric angiography as the bleeding vessels are poorly visualized on colonoscopy.

This would look for angiodysplasia, which may be associated with AS.

Resection of the diseased bowel has also been described as a treatment.

Haemodynamic optimisation prior to surgery with blood transfusion is preferred.

**Bicuspid aortic valve (BAV)****Overview:**

- It the **most common form** of **congenital** heart disease in **adults**.
- Occurs in **1-2%** of the population
- Usually **asymptomatic** in childhood
- It tends to be **sporadic** although there is a reported **familial** incidence of approximately **9%**.
- The majority eventually develop aortic stenosis or regurgitation
- Associated with:
  - A left dominant coronary circulation (the posterior descending artery arises from the circumflex instead of the RCA) and
  - Turner's syndrome.
- Around 5% of patients also have coarctation of the aorta.
- An **ejection click or sound**, best heard at the **apex**, implies that the site of the stenosis is mostly **valvular** and of **congenital** origin, that is, bicuspid valvular disease.

In a patient presenting with aortic stenosis (**AS**), what is the finding that would be most helpful in establishing a diagnosis of **congenital bicuspid valve** as the aetiology >>> An **ejection click or sound**, best heard at the **apex**.

**Complications:**

- BAV have a propensity to wear out and calcify with ageing
- Aortic stenosis/regurgitation as above
- Higher risk for aortic dissection and aneurysm formation of the ascending aorta

**TTT:** It is recorded that 1.2% per year incidence of **aortic valve replacement surgery** in individuals with BAV, although the vast majority occur in the fifth and sixth decades of life.

**Aortic regurgitation (AR)**

Features:

- 1) **Wide pulse pressure** (with low DBP)
- 2) Peripheral **vasoconstriction**, not dilatation, is typically found.
- 3) **Collapsing pulse**
- 4) Early **diastolic** murmur (a decrescendo murmur)
- 5) **Austin-Flint murmur** in severe AR:
  - It is **mid/late diastolic murmur** which may show **pre-systolic accentuation** and is virtually indistinguishable from that of mitral stenosis.
  - It is due to partial closure of the anterior mitral valve cusps caused by the regurgitation streams.
  - There is **no correlation between** the presence of murmur and severity of AR, or aetiology.
  - The first heart sound S1 is normal but in severe cases it may be absent.

**Causes (due to valve disease):**

- 1) Rheumatic fever
- 2) Bicuspid aortic valve
- 3) Infective endocarditis
- 4) Connective tissue diseases e.g. RA/SLE

**Causes (due to aortic root disease):**

- 1) Hypertension
- 2) Syphilis
- 3) Marfan's, Ehler-Danlos syndrome
- 4) Aortic dissection
- 5) Spondyloarthropathies (e.g. ankylosing spondylitis)

**NB:** Dilated cardiomyopathy >>> associated with MR not AR.

A 60-year-old man's echocardiogram shows a **dilated left ventricular (LV) cavity** with the remainder of the other chamber sizes normal >> **AR** as a **volume overload**. In AR would result in dilatation of the left ventricle.

But AS, HOCM and HTN would have the effect of causing **LV hypertrophy** and a smaller LV cavity.

**Indications for AVR in severe AR (ACC/AHA):**

- 1) All **symptomatic** patients with severe AR.
- 2) **Asymptomatic** patients with severe AR if they have **depressed LV function** (**EF < 55%**) or
- 3) **Asymptomatic** patients with severe AR if they have **severe LV dilatation** (**LVEDD >75 mm and LVESD > 55 mm**).

**NB:** Vasodilator therapy as **ACEI** or **CCB (Nifedipine)** ± **Thiazides** should be given to patients who do not have indications for AVR.

**Takayasu's arteritis**

Takayasu's arteritis is a large vessel vasculitis. It typically causes occlusion of the aorta and questions commonly refer to an absent limb pulse.

It is more common in females and Asian people.

Features:

- Systemic features of a vasculitis e.g. malaise, headache
- Unequal blood pressure in the upper limbs
- Carotid bruit
- Intermittent claudication



- Aortic regurgitation (around 20%)

Associations:

- Renal artery stenosis

Management:

- Steroids

### Tricuspid regurgitation

Signs:

- Pan-systolic murmur
- Giant V waves in JVP
- Pulsatile hepatomegaly
- Left parasternal heave

Causes:

- Right ventricular dilation
- Pulmonary hypertension e.g. COPD
- Rheumatic heart disease
- Infective endocarditis (especially intravenous drug users)
- Ebstein's anomaly
- Carcinoid syndrome

### Mitral stenosis

It is said that the causes of mitral stenosis are **rheumatic fever, rheumatic fever** and **rheumatic fever**.

Rarer causes that may be seen in the exam include mucopolysaccharidoses, carcinoid and endocardial fibroelastosis.

**Features:**

- **Mid-late diastolic rumbling** murmur (best heard in expiration)
- **With pre-systolic** accentuation
- **Loud S1**

- **Opening snap**
- Low volume pulse
- Malar flush
- Atrial fibrillation

In particular MS is **poorly tolerated** in **pregnancy** due to **volume** overload.

**Features of severe MS:**

- 1) **Increases of length** of murmur
- 2) **Opening snap** becomes **closer to S2**
- 3) **Calcification** of the valve results in >>> **immobility** and **loss of the opening snap**.

**Echocardiography:**

- The normal cross sectional area of the mitral valve is 4-6 cm<sup>2</sup>.
- A 'tight' mitral stenosis implies a cross sectional area of < 1 cm<sup>2</sup>.

**Management:**

In symptomatic MS, patient should have either balloon valvotomy or mitral valve replacement.

Most of patients can be managed with **percutaneous mitral balloon valvotomy** unless they have contraindications.

**Contraindications** for percutaneous mitral balloon valvotomy (= Indication of surgical mitral valve replacement):

- 1) Moderate to severe MR.
- 2) Heavily calcified mitral valve.
- 3) LA thrombus.
- 4) Concomitant coronary artery disease or other valve disease requiring surgery.

### Mitral regurgitation (MR)

**Myxomatous degeneration** of the mitral valve is by far the **most common** cause of MR in the United Kingdom.

The management of **severe** MR is **surgery**; either replacement or repair, depending on the anatomy.

A **percutaneous repair with clips** is possible in some patients unsuitable for conventional surgery.

Most common cause of **MS** >>> **Rheumatic fever**

Most common cause of **MR** >>> **Myxomatous degeneration**

### Rheumatic fever

The major criteria	The minor criteria
1) <b>Carditis</b> , and	1) Fever
2) <b>Polyarthrits</b>	2) Arthralgia
3) Sydenham's <b>chorea</b>	3) ↑ ESR
4) <b>Subcutaneous nodules</b> .	4) Prolonged PR interval.
5) <b>Erythema marginatum (EM)</b>	

### Pericarditis

Pericarditis is one of the differentials of any patient presenting with chest pain.

**Pericarditis = Triad of**

- 1) Chest pain worse on lying down,
- 2) Pericardial friction rub and
- 3) Classical ECG changes.

Features:

- Chest pain: may be pleuritic. It is often worse by lying down, relieved by sitting forwards.
- Other symptoms: non-productive cough, dyspnoea & flu-like symptoms.
- Pericardial rub
- Tachycardia

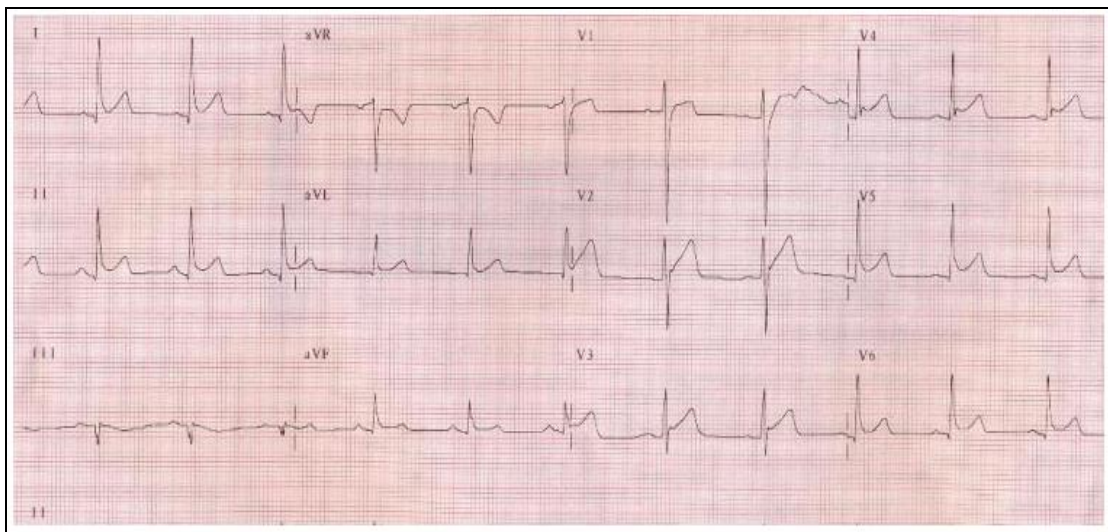
- Tachypnea
- A modest rise in troponin is in around one-third of acute pericarditis.
- Raised TLC, ESR and CPK are to be expected.

Causes:

- Viral infections: Coxsackie B virus, adenovirus, echovirus and influenza.
- TB
- Uraemia (causes 'fibrinous' pericarditis)
- Trauma
- Post-myocardial infarction, Dressler's syndrome
- Auto immune connective tissue disease: **RA**
- Malignancy
- Radiotherapy
- Hypothyroidism
- Drugs: Hydralazine

ECG changes:

- Widespread 'saddle-shaped' ST elevation (most common seen).
- PR depression: **most specific** ECG marker for pericarditis  
(PR segment **depression** in **lead II** and **elevation** in **aVR**).
- An ST/T ratio greater than 25% or a T wave amplitude of less than or equal to 3 mm also has high positive and negative predictive value in diagnosis of acute pericarditis.



TTT (If symptomatic):

- 1) **NSAIDs** (e.g. **Brufen** 800 mg 1x4)
- 2) **Colchicine** is useful both in acute episode and to prevent recurrence.
- 3) **Prednisolone** (if pain fails to settle within 48 hrs), it is considered to in patients who fail to respond to NSAIDs and colchicine.
- 4) **Pericardiectomy**: is only indicated once thorough medical therapy has failed.
- 5) Patients should be told to **reduce physical activity** for a number of days after diagnosis.

**EX:** Recurrent pericarditis with not well respond to NSAID >>> **Colchicine**

**NB:** The patient with uraemic pericarditis >>>> Haemodialysis (heparin-free) is urgently required to correct the uraemia which in turn will improve the symptoms of pericarditis.

## Myocarditis

Causes:

- Viral: Coxsackie, HIV
- Bacteria: diphtheria, clostridia
- Spirochaetes: Lyme disease
- Protozoa: Chagas' disease, Toxoplasmosis. (NO Leishmaniasis)
- Autoimmune
- Drugs: doxorubicin

**NB:** **Syphilis** involves the cardiovascular system, commonly in the form of **ascending aortic aneurysm** and **aortic regurgitation** (NOT Myocarditis).

Presentation:

- Usually young patient with acute history
- Chest pain, SOB.

## ECG: coronary territories

The table below shows the correlation between ECG changes and coronary territories:

	ECG changes	Coronary artery
<b>Anteroseptal</b>	V1-V4	Left anterior descending
<b>Inferior</b>	II, III, aVF	Right coronary
<b>High lateral</b>	I, aVL	First diagonal (D1) of LAD
<b>Lateral</b>	I, aVL +/- V5-6	<u>Left circumflex</u>
<b>Posterior</b>	Tall R in V1-2 with ST depres in V1-V4	Usually <u>left circumflex</u> , also right coronary.

These are classical **triple** effects findings of a **circumflex occlusion**. The table below shows how the changes correspond to the cardiac anatomy:

ECG changes	Component of infarction
ST elevation greater in lead II than in lead III with abnormal Q waves in II, III, and aVF	<b>Inferior</b> component of infarction
Tall R waves in V1-2, tall and pointed T waves in V1-V3	<b>Posterior</b> component of infarction
ST elevation in V5-V6	<b>Lateral</b> component of infarction

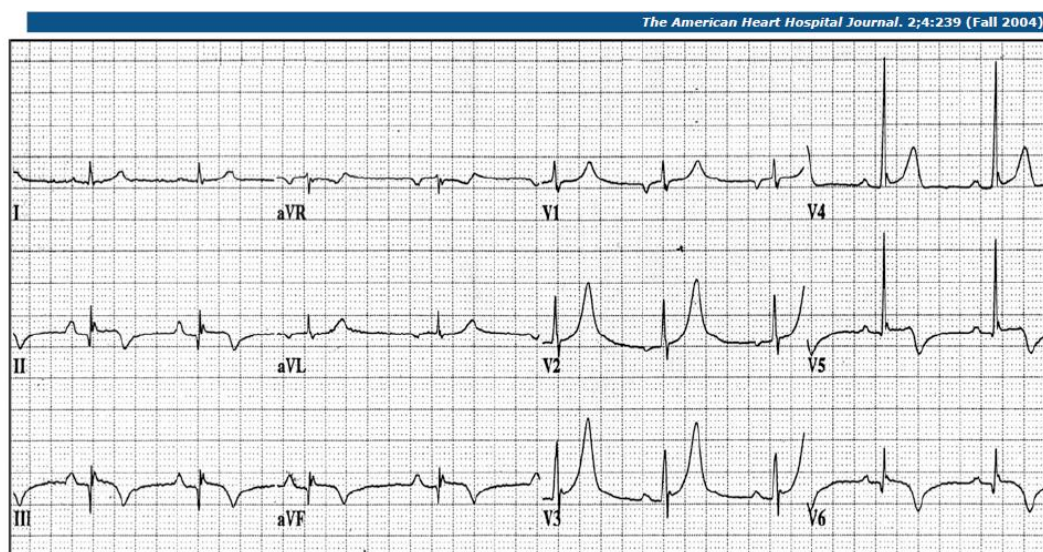
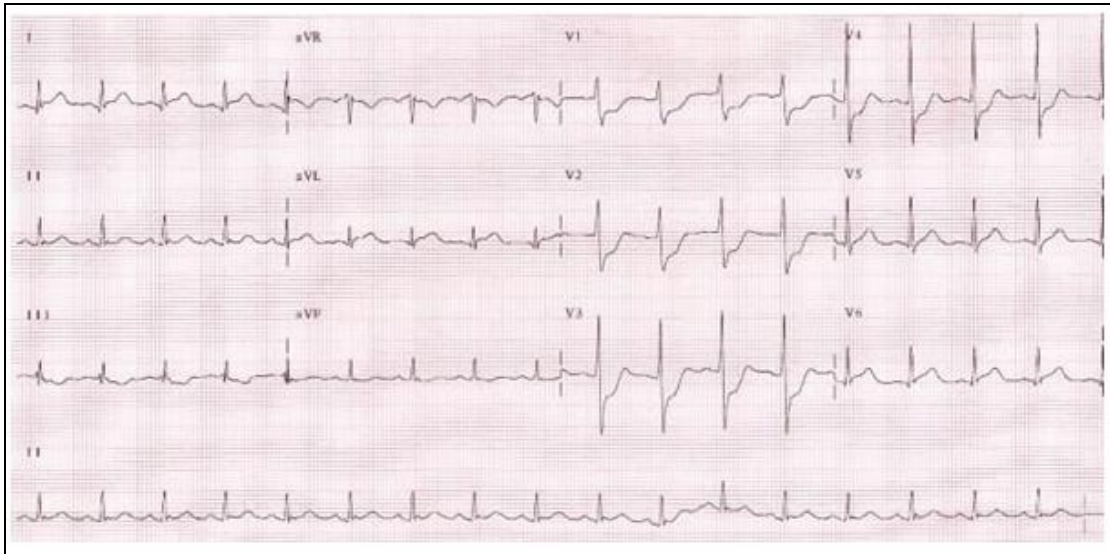


Fig: Classic ECG of Circumflex coronary artery occlusion (Inf+Post+Lat)

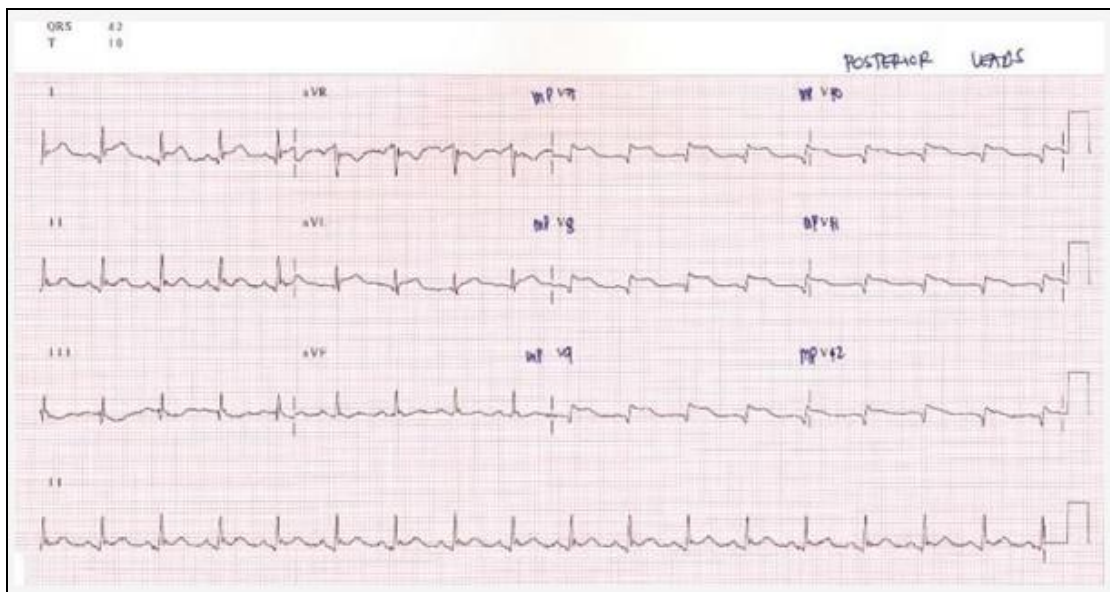


**Posterior MI:**

ECG: ST depression in V1 to V3 with upright T waves and dominant R waves (these findings are the reverse of ECG findings of anterior MI)



The diagnosis of Posterior MI can be confirmed with **ST elevation at posterior leads V7 to V9 or V12**, as shown below:



Posterior MI is usually seen in association with inferior or lateral wall MI, but can be seen **alone in about 4% of cases**.

The majority of the posterior wall is supplied by **the left circumflex artery**, with a small portion supplied by the right coronary artery.

**Coronary circulation:****Arterial supply of the heart:**

- Right aortic sinus → right coronary artery (RCA).
- Left aortic sinus → left coronary artery (LCA).
- RCA → posterior descending (in 85% it is a branch of the RCA).
- RCA supplies SA node in 60%, AV node in 90%
- LCA → LAD + circumflex
- The **left main stem** is much **shorter than 4 cm**

**Venous drainage of the heart:**

- **Coronary sinus** drains into the **right atrium (RA)**

The concept of coronary dominance refers to which coronary artery supplies **the posterior descending coronary artery**.

In the case of approximately **85%** of patients this is **the right coronary artery** with about 15% of patients having a dominant left circumflex.

The **right coronary artery** supplies the **AV node**, so **bradycardia/heart block** following **inferior MI** is common and they are not considered to be of any prognostic significance.

But if **inferior MI** with **bradycardia + junctional rhythm** with **wide QRS** (duration 160 ms) >>> indicates a more **extensive** ischaemic territory affecting the conducting bundle >>> **Temporal pacing** can be used as a holding measure to allow the myocardium time to recover.

However, **heart block** following **anterior MI** is a grave prognostic marker as this indicates a **large anterior wall extensive** infarction.

The **right coronary** system also supplies the **right ventricle**, hence problems relating to a **RV infarct** are commonly associated with an **inferior MI**.

**NB:** Pt. with MI + complete heart block >>> so, the right coronary artery is affected as it supplies the atrioventricular node (**AVN**) in **90%** of patients.

**NB:** **RCA** lesion >>> think of **4** >>> **Inferior MI ± Posterior MI ± RV infarction ± Heart block**.



**NB: Inferior MI + Complete heart block (HR 40/min) + Low BP (80/50 mmHg) + ↑ JVP >>> so RV infarction >>> TTT: IV fluids** to optimize RV filling pressure, if persistent hypotension give **inotropes**.

### **Chest pain: assessment of patients with suspected cardiac chest pain**

NICE issued guidelines in 2010 on the 'Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin'.

#### **Patients presenting with acute chest pain:**

Immediate management of suspected acute coronary syndrome (ACS):

- Glyceryl trinitrate.
- **Aspirin 300mg**. NICE do not recommend giving other antiplatelet agents (i.e. Clopidogrel) outside of hospital.
- Do not routinely give oxygen, only give if sat. < 94%\*
- Perform an ECG as soon as possible but do not delay transfer to hospital.
- **A normal ECG does not exclude ACS.**

Referral:

- Current chest pain or chest pain in the last 12 hours with an abnormal ECG: emergency admission.
- Chest pain 12-72 hours ago: refer to hospital the same-day for assessment.
- Chest pain > 72 hours ago: perform full assessment with ECG and troponin measurement before deciding upon further action

\*NICE suggest the following in terms of oxygen therapy:

**Do not routinely administer oxygen**, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:

- People with oxygen saturation (SpO<sub>2</sub>) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO<sub>2</sub> of 94-98%
- People with COPD who are at risk of hypercapnic respiratory failure, to achieve a target SpO<sub>2</sub> of 88-92% until blood gas analysis is available.

#### **Patients presenting with stable chest pain:**

With all due respect to NICE the guidelines for assessment of patients with stable chest pain are rather complicated. They suggest an approach where the risk of a patient having coronary artery disease (CAD) is calculated based on their symptoms

(whether they have typical angina, atypical angina or non-anginal chest pain), age, gender and risk factors.

NICE define anginal pain as the following:

- 1. constricting discomfort in the front of the chest, neck, shoulders, jaw or arms
- 2. precipitated by physical exertion
- 3. relieved by rest or GTN in about 5 minutes
  - patients with all 3 features have typical angina
  - patients with 2 of the above features have atypical angina
  - patients with 1 or none of the above features have non-anginal chest pain

If patients have typical anginal symptoms and a risk of CAD is greater than 90% then no further diagnostic testing is required.

It should be noted that all men over the age of 70 years who have typical anginal symptoms fall into this category.

For patients with an estimated risk of 10-90% the following investigations are recommended. Note the absence of the exercise tolerance test:

Estimated likelihood of CAD	Diagnostic testing
61-90%	<u>Coronary angiography</u>
30-60%	<u>Functional imaging</u> , for example: <ul style="list-style-type: none"> <li>• <b>Myocardial perfusion scan with SPECT.</b></li> <li>• <b>Dobutamine Stress echocardiography.</b></li> <li>• First-pass contrast-enhanced magnetic resonance (MR) perfusion</li> <li>• MR imaging for stress-induced wall motion abnormalities.</li> </ul>
10-29%	<u>CT calcium scoring</u>

If patient has symptoms suggestive of IHD with normal ECG, the diagnosis should be confirmed with non-invasive functional scanning such as myocardial perfusion scan with SPECT.

According to NICE guidance, where the diagnosis of CAD is suspected but not confirmed, exercise testing is no longer recommended.

**NB: Exercise ECG is not useful in patients with:**

- 1) Conduction abnormalities: e.g. RBBB.
- 2) Resting ECG abnormalities like ST segment depression of > 1 mm.
- 3) WPWS
- 4) Those with ventricular pacing rhythm.
- 5) Those on digoxin.

**Pharmacological stress in form of dobutamine stress echocardiography** can be used in patients who are unable to exercise because of stroke, PVD or arthritis, although it also should be avoided in conduction abnormalities, resting ECG ischaemic abnormalities and WPWS.

When comparing the dobutamine stress versus thallium scanning, **thallium has greater sensitivity**, versus **greater specificity for dobutamine** with respect to CAD.

So in a case of intermediate likelihood CAD, thallium is the preferred option.

### **Angina pectoris: drug management**

The management of stable angina comprises lifestyle changes, medication, percutaneous coronary intervention and surgery.

Medication:

- All patients should receive aspirin and a statin in the absence of any contraindication.
- Sublingual glyceryl trinitrate to abort angina attacks.
- NICE recommend using either a beta-blocker or a calcium channel blocker first-line based on 'comorbidities, contraindications and the person's preference'.
- If a calcium channel blocker is used as monotherapy a rate-limiting one such as verapamil or diltiazem should be used.
- If a CCB is used in combination with a beta-blocker then use a long-acting dihydropyridine calcium-channel blocker (e.g. modified-release nifedipine).
- Remember that beta-blockers should not be prescribed concurrently with verapamil (risk of complete heart block) and diltiazem should be used with caution due to the risk of bradycardia.
- Verapamil and diltiazem should be avoided with  $\beta$ B and with pt. has CHF.

- If there is a poor response to initial treatment then medication should be increased to the maximum tolerated dose (e.g. for **atenolol** 100 mg OD, however, **Fatigue** is a frequent side effect of atenolol which typically is felt **2 hours** and beyond **after** taking the drug.).
- If a patient is still symptomatic after monotherapy with a beta-blocker add a calcium channel blocker and vice versa.
- If a patient is on monotherapy and cannot tolerate the addition of a calcium channel blocker or a beta-blocker then consider one of the following drugs: a long-acting nitrate, ivabradine, nicorandil or ranolazine.
- Nicorandil is a Potassium-channel activator.
- If a patient is taking both a beta-blocker and a calcium-channel blocker then only add a third drug whilst a patient is awaiting assessment for PCI or CABG.

Nitrate tolerance:

- Many patients who take nitrates develop tolerance and experience reduced efficacy.
- The BNF advises that patients who develop tolerance should take the second dose of isosorbide mononitrate after 8 hours, rather than after 12 hours. This allows blood-nitrate levels to fall for 4 hours and maintains effectiveness
- This tolerance effect is not seen in patients who take modified release isosorbide mononitrate (Imdur®).
- The starting dose of isosorbide mononitrate is 10mg bid.

#### **Ivabradine (Procoralan ®):**

- A new class of anti-anginal drug which works by reducing the heart rate.
- It acts on the I<sub>f</sub> ('funny') ion current which is highly expressed in the sinoatrial node (SAN), reducing cardiac pacemaker activity.
- Adverse effects: visual effects, particular luminous phenomena, are common. Bradycardia, due to the mechanism of action, may also be seen.
- There is no evidence currently of superiority over existing treatments of stable angina.

<b>NB:</b> EX. Pt. with IHD with angina attacks: <b>ASA + Statin + Atenolol</b> 100 md OD + <b>Nifedipine</b> MR 30mg OD ± <b>Isosorbide mononitrate</b> is 10mg bid ± <b>Ivabradine</b> ± <b>Nicorandil</b> .
--

<b>NB:</b> EX: Pt. with <u>Prinzmetal's angina</u> >>> treatment = <u>dihydropyridine</u> calcium channel blocker e.g. <u>Felodipine</u> .
--

**Non-atherosclerotic angina** would be associated with conditions such as

- 1) Anaemia
- 2) Thyrotoxicosis
- 3) Aortic stenosis
- 4) Aortic regurgitation
- 5) HOCM

### **Myocardial infarction: management**

A number of studies over the past 10 years have provided an evidence for the management of ST-elevation myocardial infarction (STEMI).

In the absence of contraindications, all patients should be given:

- 1) Aspirin
- 2) Clopidogrel:
- 3) LMWH

NICE suggest the following in terms of oxygen therapy:

**Do not routinely administer oxygen**, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:

- People with oxygen saturation (SpO<sub>2</sub>) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO<sub>2</sub> of 94-98%
- People with COPD who are at risk of hypercapnic respiratory failure, to achieve a target SpO<sub>2</sub> of 88-92% until blood gas analysis is available.

Primary percutaneous coronary intervention (**PCI**) has emerged as **the gold-standard treatment for STEMI** but is not available in all centres.

Thrombolysis should be performed in patients without access to primary PCI.

With regards to thrombolysis:

- Tissue plasminogen activator (**tPA**) has been shown to offer clear mortality benefits over streptokinase.
- Tenecteplase is easier to administer and has been shown to have non-inferior efficacy to alteplase with a similar adverse effect profile.

An ECG should be performed 90 minutes following thrombolysis to assess whether there has been a greater than 50% resolution in the ST elevation.

- If there has not been adequate resolution then rescue PCI is superior to repeat thrombolysis.
- For patients successfully treated with thrombolysis, PCI has been shown to be beneficial. The optimal timing of this is still under investigation.

In pt. with STEMI due to; **Cocaine** which is a drug of widespread abuse and remains one of the commonest causes of acute MI in men **below 35 years of age**. Cocaine-induced MI is thought to be related to **coronary artery spasm** as many patients do not have overt coronary artery disease. It is probably caused by stimulation of the  $\alpha$ -adrenergic receptors in smooth muscle cells. In addition, cocaine increases endothelin-1 (a VC) and decreases nitric oxide (VD).

Consequently guidelines suggest the use of **IV nitrates (GTN)** in the **first** instance coupled with **calcium antagonists**. **Benzodiazepines IV** are also effective in resolving chest pain and improving cardiac performance. If there is no improvement in the clinical condition, **then angiography** should be considered. **Thrombolytic are generally avoided.**

Also it is important to **avoid beta-blockers** in treating cocaine-induced chest pains or acute MI, as this may result in unopposed alpha 1 adrenergic action with worsening coronary spasm.

### **Thrombolysis**

ECG criteria for thrombolysis within 24 hours of typical pain include:

- 1) **ST elevation** of more than **1 mm** in standard **limb** leads
- 2) **ST elevation** more than **2 mm** in anterior **chest** leads, and
- 3) **New left bundle branch block (LBBB).**

Thrombolytic drugs activate plasminogen to form plasmin. This in turn degrades fibrin and help breaks up thrombi. They in primarily used in patients with STEMI.

Other indications include acute ischaemic stroke and acute pulmonary embolism with unstable haemodynamic, although strict inclusion criteria apply.

Examples:

- Streptokinase
- **Alteplase**
- Tenecteplase

**Contraindications to thrombolysis:**

- 1) **Active internal bleeding** (menses excluded).
- 2) **GIT bleeding** within the past **month**.
- 3) Coagulation and bleeding disorders.
- 4) Major trauma, major surgery or head injury **within 3 wks**.
- 5) Recent significant head injury
- 6) CNS neoplasm
- 7) Previous haemorrhagic stroke at any time
- 8) Ischaemic stroke < 3 months
- 9) Prolonged cardiopulmonary resuscitation (CPR) (> half an hour).
- 10) Known or suspected **Aortic dissection**
- 11) Pregnancy
- 12) Severe uncontrolled hypertension
- 13) Proliferative diabetic retinopathy: is **relative** contraindications.
- 14) Allergy and oral anticoagulants: are **relative** contraindications.

Those patients over 75 years benefit from thrombolysis as much or more than younger patients with MI.

Side-effects:

- Haemorrhage
- Hypotension - more common with streptokinase
- Allergic reactions may occur with streptokinase

**Percutaneous coronary intervention (PCI)**

Percutaneous coronary intervention (PCI) is a technique used to restore myocardial perfusion in patients with ischaemic heart disease, both in patients with stable angina and acute coronary syndromes.

Stents are implanted in around 95% of patients - it is now rare for just balloon angioplasty to be performed.

Following stent insertion migration and proliferation of smooth muscle cells and fibroblasts occur to the treated segment. The stent struts eventually become covered

by endothelium. Until this happens there is an increased risk of platelet aggregation leading to thrombosis.

Two main complications may occur:

- **Stent thrombosis:** due to platelet aggregation as above. Occurs in 1-2% of patients, most commonly in the first month. Usually presents with acute myocardial infarction.
- **In-stent Restenosis (ISRS):** due to excessive tissue proliferation around stent. Occurs in around 5-20% of patients, most commonly in the first 3-6 months. Usually presents with the recurrence of angina symptoms. Risk factors include diabetes, renal impairment and stents in venous bypass grafts.

Types of stent:

- Bare-metal stent (BMS)
- Drug-eluting stents (DES): stent coated with paclitaxel or rapamycin which inhibit local tissue growth. Whilst this reduces restenosis rates the stent thrombosis rates are increased as the process of stent endothelialisation is slowed.

Following insertion the most important factor in preventing stent thrombosis is antiplatelet therapy. Aspirin should be continued indefinitely. The length of clopidogrel treatment depends on the type of stent, reason for insertion and consultant preference.

Studies have shown that in patients with type-2 diabetes, coronary stents are liable to re-stenosis at a rate of 40–50% by the end of a 6-month follow-up period. Drug eluting stents have been shown to reduce the relative risk of re-stenosis by around 80%, but only where dual anti-platelet therapy with clopidogrel and aspirin is continued for at least 1 year. Pioglitazone has been shown to reduce in stent re-stenosis, but given it is a cause of fluid retention and may worsen heart failure, any effect on stent re-stenosis is subsidiary to increased risk of heart failure.

Percentage of **uncoated** stents **ISRS** with **DM T2** by **6 months** >>> **45%**

### **Cholesterol embolisation syndrome**

Overview:

- It is most commonly seen in patients with **existing arterial disease** who have undergone arterial **manipulation**.
- Seen more commonly in **arteriopathies**, abdominal aortic aneurysms.



- Pre-existing renal impairment, DM and hypovolaemia at time of procedure are all associated with **increased risk**.
- Cholesterol emboli may break off causing renal disease.
- Ulceration of an **atheromatous plaque** of the **abdominal aorta** especially in **elderly** patient >> embolus in his femoral artery >> absent leg pulse.
- Its data are largely based on post mortem examinations.
- Some studies suggest that as many as **25-30%** of patients undergoing angiography will have atherosclerotic emboli.

Features:

- 1) **Eosinophilia** (present in 70% of cases)
- 2) **Purpura**
- 3) **Livedo reticularis**
- 4) **Renal failure**
- 5) **Acute abdomen** due to bowel ischaemia.

**TTT:** Unfortunately there is **no specific treatment** shown to be of benefit.

**EX:** A 62-year-old male is admitted with an inferior MI and receives thrombolysis. His ECG shows good ST segment resolution. The following day he develops some **pain** in the **legs** and a **dusky discolouration** of the lower limbs. On closer examination there is a **diffuse petechial rash** over the lower legs, particularly the **feet**, with **raised TLC - marked eosinophilia**, raised **ESR**, raised **IgE** and **low** complement. But **all peripheral pulses are palpable** >> **Cholesterol embolisation syndrome**. Peripheral pulses are intact because cholesterol emboli are **microcrystals** which are too small to occlude medium sized arteries.

### **Fat embolism syndrome**

Fat embolism syndrome is a **clinical** diagnosis secondary to the presence of fat globules in the lung parenchyma and circulation that are typically released following **long bone fractures**.

It requires **high index of suspicion** and usually presents **12-72 hours after initial injury**.

There is a classic triad of:

- 1) **Respiratory** changes - Dyspnoea, tachypnoea and hypoxaemia are early findings. These may progress to respiratory failure and ARDS requiring mechanical ventilation.

- 2) **Neurological** features - Cerebral emboli produce neurological signs in up to 86% cases. They often occur after onset of respiratory symptoms, with a wide spectrum ranging from mild confusion and drowsiness to seizures. Usually there is an acute confusional state with or without focal signs. Most neurological deficits are transient and reversible.
- 3) **Petechial** rash - This is the final component of the triad to develop and occurs in 60% of cases. Rash is seen in the conjunctiva, mucous membranes, skin folds of upper body particularly neck and axilla, appearing within the first 36 hours.

Patients may also develop:

- Pyrexia
- Tachycardia
- ECG changes (ST segment depression and right heart strain)
- Fluffy retinal exudates
- Coagulopathy, and
- Renal changes (oliguria, lipiduria, proteinuria or haematuria).

#### **Laser transmyocardial revascularisation**

Open chest surgery is undertaken, during which **laser holes** are punched from the **epicardial** surface into areas of suspected ischaemic or hibernating ventricular muscle so **damages the endocardium**. The process is not fully understood.

The epicardial end of the hole heals up leaving artificial channels communicating with the ventricular chamber and effectively forming new coronary vessels.

Laser transmyocardial revascularisation has potential in **distal** disease as **DM**.

**Angioplasty** and **CABG** are useful in **proximal** disease.

#### **Acute coronary syndrome: management of NSTEMI**

Symptoms which may indicate ACS include:

- **Pain** in the chest and/or other areas (e.g. arms, back or **jaw**) lasting **longer than 15 minutes**.
- Chest pain associated **with nausea and vomiting**, marked **sweating**, breathlessness, haemodynamic instability.
- New onset chest pain, or abrupt deterioration in previously stable angina, with recurrent chest pain occurring frequently and with little or no exertion, and with episodes often lasting longer than 15 minutes.

NICE produced guidelines in 2010 on the management of unstable angina and non-ST elevation myocardial infarction (NSTEMI). They advocate managing patients based on the early risk assessment using a recognised scoring system such as GRACE (Global Registry of Acute Cardiac Events) to calculate a predicted 6 month mortality.

All patients should receive:

- Aspirin 300mg
- Nitrates or morphine to relieve chest pain if required

Whilst it is common that non-hypoxic patients receive oxygen therapy there is little evidence to support this approach.

The 2008 British Thoracic Society oxygen therapy guidelines advise not giving oxygen unless the patient is hypoxic.

**Antithrombin** treatment. **Fondaparinux** should be offered to patients who are not at a high risk of bleeding and who are not having angiography within the next 24 hours. If angiography is likely within 24 hours or a patients creatinine is > 265 µmol/l unfractionated heparin should be given.

**Clopidogrel** 300mg should be given to patients with a predicted 6 month mortality of more than 1.5% or patients who may undergo percutaneous coronary intervention within 24 hours of admission to hospital. Clopidogrel should be continued for 12 months.

Intravenous **glycoprotein IIb/IIIa receptor antagonists** (eptifibatide or tirofiban) should be given to patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%), and who are scheduled to undergo angiography within 96 hours of hospital admission.

**Coronary angiography** should be considered within 96 hours of first admission to hospital to patients who have a predicted 6-month mortality above 3.0%. It should also be performed as soon as possible in patients who are clinically unstable.

The table below summaries the mechanism of action of drugs commonly used in the management of acute coronary syndrome:

Medication	Mechanism of action
<b>Aspirin</b>	Antiplatelet - inhibits the production of <b>thromboxane A2</b>
<b>Clopidogrel</b>	Antiplatelet - inhibits <b>ADP</b> binding to its platelet receptor
<b>Enoxaparin</b>	<b>Activates antithrombin III</b> , which in turn potentiates the inhibition of coagulation factors <b>Xa</b>
<b>Fondaparinux</b>	<b>Activates antithrombin III</b> , which in turn potentiates the inhibition of coagulation factors <b>Xa</b>
<b>Bivalirudin</b>	<b>Reversible direct thrombin inhibitor</b>

NICE guidelines of NSTEMI/UA are based **on 6 month mortality risk:**

- **If > 1.5%** >>> Clopidogrel for 12 months.
- **If > 3%** >>>> IV GP IIb/IIIa receptor antagonists + Coronary angiography within 96 hours.

**EX:** Patient at CCU post-acute **MI** with **PCI** and **stent** and he is on ASA + Plavix + Clexane, now he has melena, drop of BP with postural hypotension and low Hb >>> after giving IV fluids and packed RBCs transfusion >>> **Stop anticoagulant, but keep both ASA and Plavix.**

يوقف الكلوكسان فقط .... وتستمر مضادات الصفائح الدموية الاثنين معا

Management of anti-platelet agents and anti-coagulation is a source of considerable debate when haemorrhage is seen post PCI.

In this case a significant upper GIT haemorrhage has occurred, and therefore **stopping clexane is most appropriate.**

Stopping both anti-coagulation and anti-platelet medication together significantly increases the risk of in-stent thrombosis occurring.

Even stopping one or both anti-platelet agents would carry an unacceptable level of risk so soon after PCI, and is therefore best avoided if possible.

### Myocardial infarction: secondary prevention

NICE produced guidelines on the management of patients following a MI in 2007. Some key points are listed below:

All patients should be offered the following drugs:

- ACE inhibitor
- Beta-blocker
- Aspirin
- Statin

### Clopidogrel:

- Since Clopidogrel came off patent it is now much more widely used post-MI.
- STEMI: the European Society of Cardiology recommend dual antiplatelets for 12 months. In the UK this means aspirin + Clopidogrel
- NSTEMI: following the 2010 NICE unstable angina and NSTEMI guidelines clopidogrel should be given for the first 12 months if the 6 month mortality risk is > 1.5% (this “The 6 month mortality” may be calculated using a validated risk model such as GRACE).
- The AHA/ACC/SCAI/ACS/ADA published recommendations in 2007 stressed the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent (DES).
- **Even you should postpone any elective operations rather than to stop the dual antiplatelet therapy.**

### Aldosterone antagonists:

- Patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-MI treatment (e.g. eplerenone) should be initiated within 3-14 days of the MI, preferably after ACE inhibitor therapy.

Any Pt. Post MI >>>>> ACEI +  $\beta$ B + ASA + Plavix + Statins  $\pm$  Aldactone

NICE guidelines on MI: secondary prevention (CG48) recommend a number of lifestyle modifications as prevention. These include **increasing physical activity to 20-30 minutes per day**.

## Myocardial infarction: complications

Patients are at risk of a number of immediate, early and late complications following a myocardial infarction (MI).

### Cardiac arrest:

This most commonly occurs due to patients developing ventricular fibrillation (VF) and is the most common cause of death following a MI. Patients are managed as per the ALS protocol with defibrillation.

### Cardiogenic shock:

If a large part of the ventricular myocardium is damaged in the infarction the ejection fraction of the heart may decrease to the point that the patient develops cardiogenic shock (=biventricular failure with low BP). This is difficult to treat. Other causes of cardiogenic shock include the 'mechanical' complications such as left ventricular free wall rupture as listed below.

In cardiogenic shock >>> cardiac index below 2 L/min/m<sup>2</sup>

Patients may require inotropic (Dopamine) support and/or an Intra-Aortic Balloon Counter Pulsation (IABCP).

Cardiogenic shock >> **ATN** >> acute renal failure.

### TTT of cardiogenic shock (APO) as by AHA-ACLS:

#### First step:

- High flow O<sub>2</sub>
- Lasix 1mg/kg IV
- Morphine 2-4 mg IV
- GTN SL

#### Second step (guide by SBP):

- SBP > 100 mmHg >>> **GTN IVI** 10-20 Mcg/min.
- SBP 70-100 mmHg with No signs or symptoms of shock >>> **Dobutamine IVI** 2-20 Mcg/kg/min.
- SBP 70-100 mmHg with signs or symptoms of shock >>> **Dopamine IVI** 5-15 Mcg/kg/min.
- SBP < 70 mmHg with signs or symptoms of shock >>> **Noradrenaline IVI** 0.5-30 Mcg/min

Crucial to prognosis is haemodynamic stabilisation, and in this case with hypotension and shock, **IABCP to support cardiac output is the best approach.**

Balloon inflation is timed with **diastole**; **once closure of the aortic valve** has occurred; this corresponds to the **middle of the T wave**. For blood to be ejected antegrade to perfuse the tissues and retrograde to perfuse the coronaries the aortic valve must be closed and competent.

Aortic regurgitation is therefore a contraindication to placement of an intra-aortic balloon pump.

Inotropes such as adrenaline and noradrenaline can significantly increase myocardial ischaemia, as such they would only be adjunctive support after IABCP.

Whilst vasodilators such as GTN can significantly improve myocardial blood flow, they are inappropriate here because of hypotension.

### **Chronic heart failure:**

As described above, if the patient survives the acute phase their ventricular myocardium may be dysfunctional resulting in chronic heart failure. Loop diuretics such as furosemide will decrease fluid overload. Both ACE-inhibitors and beta-blockers have been shown to improve the long-term prognosis of patients with chronic heart failure.

### **Tachyarrhythmias:**

Ventricular fibrillation, as mentioned above, is the most common cause of death following a MI. Other common arrhythmias including ventricular tachycardia.

**Post MI ventricular tachycardia (VT)** is most commonly due to **scar** tissue. It may also be related to ischaemia.

The definitive investigation would be **Electrophysiological study EPS** due to the fact that if this were **scar-related VT** the site could be localised and even possibly **ablated**. If not, then an implantable cardio-defibrillator (**ICD**) implantation may be considered.

The development of VT/VF in the **first** day following an acute MI >>> is thought to be of **no prognostic significance** if dealt with promptly either by DC or medically by amiodarone 200 mg 1x3.

However, the **late** development of VT/VF in the context of a full thickness myocardial scar, as evidenced by Q waves on the ECG, carries a **very poor prognosis**. And so **ICD** has been shown to offer improved survival over anti-arrhythmic therapy. Amiodarone would be an appropriate choice in patients who are unsuitable for ICD insertion.

The development of late onset VT following an ischaemic event (Acute MI) coupled with LV impairment on echo >>> is an indication for ICD.

**EX:** Pt with MI and developed a broad spectrum tachycardia **after 1 month** of MI with Q waves in ECG >>> TTT is **ICD**, not amiodarone tab

**Brady arrhythmias:**

Atrioventricular block is more common following inferior MI.

**Pericarditis:**

Pericarditis in the first 48 hours following a large transmural MI is common (c. 10% of patients).

The pain is typical for pericarditis (worse on lying flat, radiation to the trapezius edge etc.), a pericardial friction rub may be heard and a pericardial effusion may be demonstrated with an echocardiogram.

It is usually managed by **increase aspirin to 650 mg every 4 hr** and analgesia like paracetamol.

Anticoagulant can be continued if there is no pericardial effusion, as in such cases the risk of haemorrhagic pericarditis is low. However in the presence of significant effusion or if the effusion is increasing, heparin/LMWL should be discontinued.

**Cardiac tamponade:** is a known complication of acute MI, the clue of diagnosis is sudden onset dyspnoea with clear lung fields, cardiogenic shock and electrical alternans, consistent with ventricular rupture.

TTT: the definitive ttt is pericardiocentesis with emergency ventricular repair, if haemodynamically unstable >>> IV Inotropes + arrange for insertion of IABP (Intra-aortic balloon pump) + colloids to establish the patient before pericardiocentesis takes place.

**Dressler's syndrome:** tends to occur around 2-6 weeks following a MI. The underlying pathophysiology is thought to be an autoimmune reaction against antigenic proteins formed as the myocardium recovers. It is characterised by a combination of fever, pleuritic pain, pneumonitis, pericardial effusion and a raised ESR. It is treated with aspirin in large doses or NSAIDs not steroid. If recurrent colchicine can be used, pericardiocentesis can be required in rare cases.

ECG: tall R in V1 and V2.

CXR: Cardiomegaly ± pleural effusion

**Left ventricular aneurysm:**

The ischaemic damage sustained may weaken the myocardium resulting in aneurysm formation. This is typically associated with persistent ST elevation and left ventricular failure. Thrombus may form within the aneurysm increasing the risk of stroke. Patients are therefore anticoagulated.



**Left ventricular free wall rupture:**

This is seen in around 3% of MIs and occurs around 1-2 weeks afterwards. Patients present with acute heart failure secondary to cardiac tamponade (raised JVP, pulsus paradoxus, diminished heart sounds). Urgent pericardiocentesis and thoracotomy are required.

**Ventricular septal rupture:**

Rupture of the interventricular septum usually occurs in the **first week** and is seen in around **1-2%** of patients. The average time from MI to rupture has been reported to be between 2 and 4 days, but it may be as short as a **few hours** or as long as 2 weeks. It occurs most commonly after **anterior MI**. Features: **acute heart failure with low BP and tachycardia** associated with a **pan-systolic murmur**. An **echocardiogram** is diagnostic and will exclude acute mitral regurgitation which presents in a similar fashion. **Mortality is very high. Urgent surgical correction** is needed.

**Acute mitral regurgitation:**

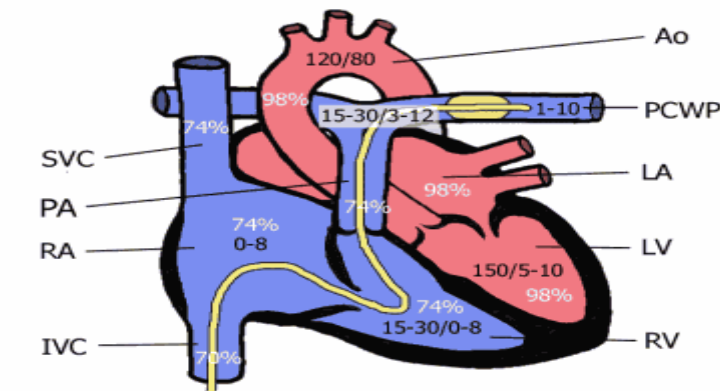
More common with **infero-posterior** infarction and may be due to ischaemia or **rupture of the papillary muscle**. An early-to-mid **systolic** murmur is typically heard radiated into the axilla with **associated pulmonary oedema** due to **mitral valve prolapse**. Patients are treated with vasodilator therapy like ACEI and diuretics but often require **emergency surgical repair**.

Pt with **MI >>> suddenly develops pulmonary oedema** and a **loud systolic murmur >>>** this is due to **acute left ventricular failure (LVF)** with mitral valve prolapse (MVP) ± ventricular septal defect (VSD). >>> So do **Right heart catheterisation and oximetry**.

**NB:** The post-MI ventricular septal defect (VSD) or post-MI rupture of papillary muscle (causing acute mitral regurgitation).

VSD and papillary rupture are difficult to distinguish clinically. The diagnosis is established by **demonstration of a left to right shunt**.

The presence of a **VSD** would be confirmed by **detecting a step-up in the oxygen saturation between the RA and PA**; if there is no step-up, the diagnosis is probably papillary muscle rupture.



**Cardiac catheter data**  
**Normal cardiac pressures & oxygen saturation**

	End systolic (mmHg)	End diastolic (mmHg)	Mean	O <sub>2</sub> saturation
<b>Left heart</b>				
Aorta	120	80	95	98%
LV	150	5-10		98%
LA				98%
<b>Right heart</b>				
RA			0-8	74%
RV	15-30	0-8		74%
PA	15-30	3-12	9-16	74%
SVC				74%
IVC				70%
PCWP			1-10	

**NB:** The most specific finding for a diagnosis of myocardial infarction is >> **Evolution of Q waves on ECG.**

- **The evolution of Q waves** is the most suggestive of an infarct. A Q wave is any negative deflection that precedes an R wave on the ECG. Small Q-waves are normal in most leads, and they can be prominent in leads III and aVR as a normal variant, but should not be seen in leads V1-V3. They are considered **pathological** if they are **more than 1mm wide, more than 2mm deep, more than 25% of the depth of the QRS complex, or seen in leads V1-V3**. Such pathological Q-waves usually indicate prior full thickness myocardial infarct.
- Cardiac enzymes may be elevated in pulmonary embolism (PE), renal failure and sepsis. It is increasingly recognised that raised troponin is not specific to myocardial ischaemia, and therefore must be interpreted in the context of the clinical history.
- Raised ST segments can be associated with conditions such as pericarditis, and is again not specific for myocardial ischaemia.
- As any medical doctor on call knows, severe chest pain has a vast number of differential diagnoses.
- Akinetic wall motion on the echo may occur with any regional disease process like amyloid, etc.

## Heart block (HB)

### Features:

- Syncope
- Regular bradycardia (30-50 bpm)
- Heart failure
- Wide pulse pressure
- JVP: cannon waves in neck
- Variable intensity of S1

### Types of heart block:

#### First degree heart block:

- PR interval > 0.2 seconds.

#### Second degree heart block:

- Type 1 (Mobitz I, Wenckebach): progressive prolongation of the PR interval until a dropped beat occurs.
- Type 2 (Mobitz II): PR interval is constant but the P wave is often not followed by a QRS complex.

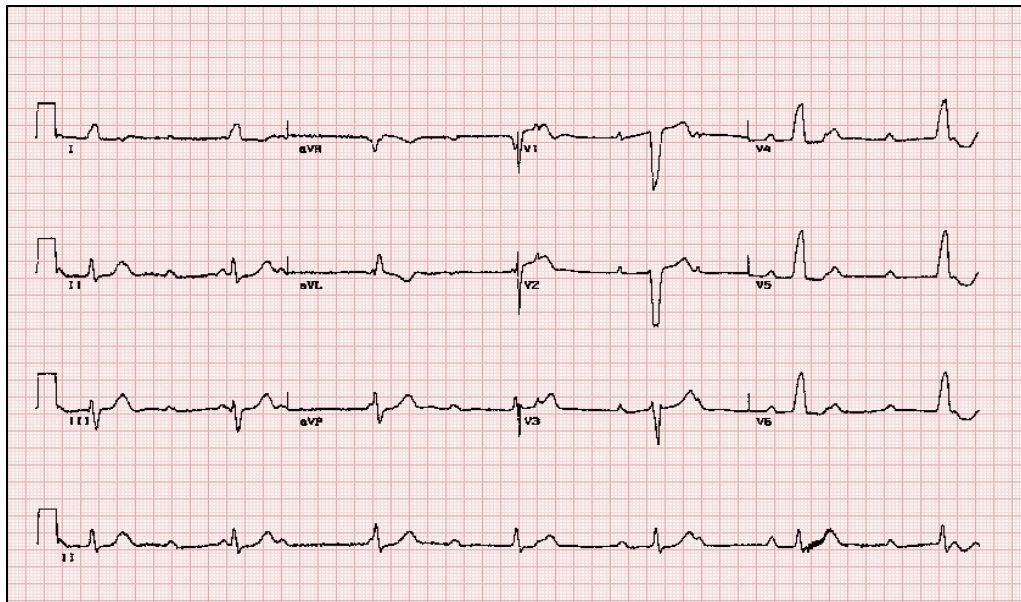
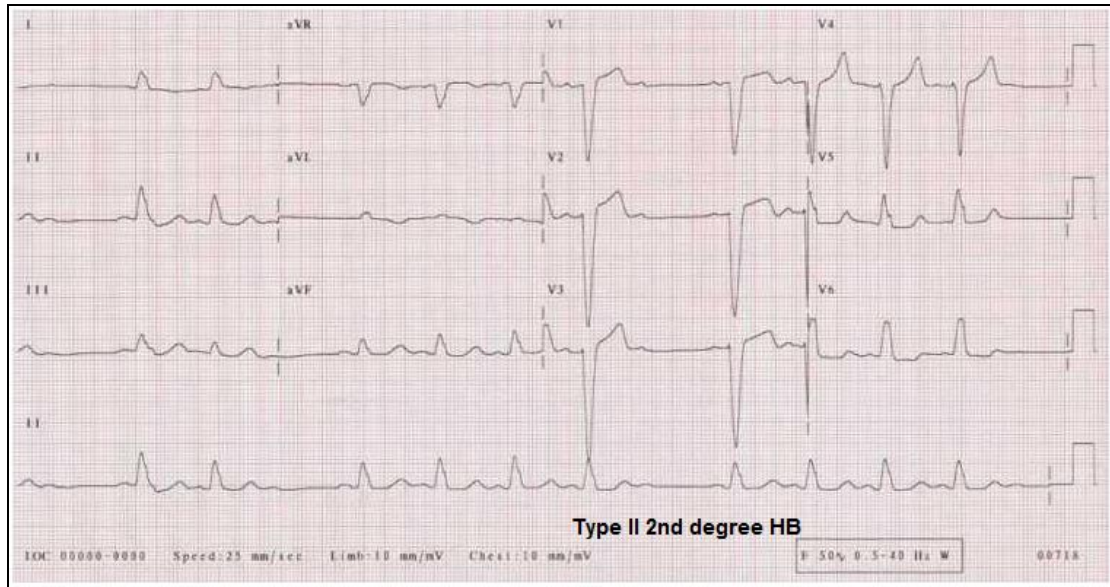
#### Third degree (complete) heart block:

- There is no association between the P waves and QRS complexes.

**Mobitz type II or complete heart block** does **not** respond to atropine >>> the optimal ttt is **Trans-venous permanent pacing**.

Atropine may be useful for sinus or junctional bradycardia.

Complete heart block following a MI >>> so, **Right** coronary artery lesion.



**CHB:** There are P waves which show no relation to the QRS complexes. The QRS complexes are wide, regular and represent a ventricular escape rhythm.

**NB:** The atrioventricular node (AVN) is supplied by the posterior interventricular artery, which in the majority of patients is a branch of the right coronary artery. In the remainder of patients the posterior interventricular artery is supplied by the left circumflex artery.

**NB:** Second degree (Type 2) and third degree HB >>> **Permanent pacing.**

## Clopidogrel

Clopidogrel is an antiplatelet agent used in the management of cardiovascular disease. It was previously used **when aspirin was not tolerated** or **contraindicated** but there are now a number of conditions for which clopidogrel is used in addition to aspirin, for example in patients with an ACS.

Following the NICE technology appraisal clopidogrel is also **now first-line** in patients following an ischaemic stroke and in patients with peripheral arterial disease.

Clopidogrel belongs to a class of drugs known as **thienopyridines** which have a similar mechanism of action. Other examples include:

- Prasugrel
- Ticagrelor
- Ticlopidine

Mechanism:

- **Antagonist** of the P2Y<sub>12</sub> adenosine diphosphate (**ADP**) **receptor**, inhibiting the activation of platelets

Interactions:

- Concurrent use of proton pump inhibitors (PPIs) may make clopidogrel less effective (MHRA July 2009).
- This advice was updated by the MHRA in April 2010, evidence seems inconsistent but **omeprazole** and **esomeprazole** still cause for concern. Other PPIs such as *lansoprazole should be OK.*

**NB:** **TTP** (thrombotic thrombocytopenic purpura) can occur in **less than 1%** of patients receiving **clopidogril** or ticlopidine >>> **peripheral blood film >>> fragmented RBCs.**

**EX:** Pt after 2 weeks from PCI and Plavix usage, develop Rt. sided weakness, bleeding tendency, low platelets, anaemia, renal impairment, fever, Disturbed LOC with confusion >>> **TTP due to clopidogril.**

## Acute coronary syndrome: prognostic factors

The 2006 Global Registry of Acute Coronary Events (GRACE) study has been used to derive regression models to predict death in hospital and death after discharge in patients with acute coronary syndrome.

Poor prognostic factors:

- Age
- Development (or history) of heart failure
- Peripheral vascular disease
- Reduced systolic blood pressure
- Killip class (see below)
- Initial serum creatinine concentration
- Elevated initial cardiac markers
- Cardiac arrest on admission
- ST segment deviation

**Killip class:** system used to stratify risk post myocardial infarction:

Killip class	Features	30 day mortality
I	No clinical signs heart failure	6%
II	Lung crackles, S3	17%
III	Frank pulmonary oedema	38%
IV	Cardiogenic shock	81%

### Renal vascular disease

Renal vascular disease is most commonly due to **atherosclerosis** (> 95% of patients). It is associated with risk factors such as **smoking** and **hypertension** that cause atheroma elsewhere in the body. It may present as hypertension, chronic renal failure or **'flash' pulmonary oedema**.

In younger patients however fibromuscular dysplasia (**FMD**) needs to be considered. FMD is more common in young women and characteristically has a 'string of beads' appearance on angiography. Patients respond well to balloon angioplasty

Investigation:

- **MRA angiography** is now the investigation of choice
- CT angiography



- Conventional renal angiography is less commonly performed used nowadays, but may still have a role when planning surgery

Flash pulmonary oedema, U&Es worse on ACE inhibitor, asymmetrical kidneys → **renal artery stenosis (RAS)** - do **MRA** angiography.

**Flash pulmonary oedema** in someone with a history of **hypertension**, especially those suspected of being arteriopathies such as **smokers**, should raise the possibility of **renal artery stenosis**.

### Down syndrome (Trisomy 21): features

#### Clinical features:

- Face: upslanting palpebral fissures, epicanthic folds, Brushfield spots in iris, protruding tongue, small ears, round/flat face
- Flat occiput
- Single palmar crease, pronounced 'sandal gap' between big and first toe
- Hypotonia
- **Congenital heart defects (40-50%)**
- **GIT malformations (6%):**
  - **Duodenal atresia** ('double bubble' sign.)
  - **Hirschsprung's disease**

**Cardiac complications:** (Multiple cardiac problems may be present):

- 1) **Endocardial cushion defect** (c. **40%**, also known as **complete atrioventricular septal canal defects**)
- 2) VSD (c. 30%)
- 3) Secundum ASD (c. 10%)
- 4) Tetralogy of Fallot (c. 5%)
- 5) Isolated PDA (c. 5%)

#### **Later complications:**

- Fertility problems:
  - **Males** are almost always **infertile** due to impaired spermatogenesis.
  - **Females** are usually **subfertile**, and have an increased incidence of problems with pregnancy and labour.

- Learning difficulties
- **Short stature**
- Repeated respiratory infections (+hearing impairment from glue ear)
- Acute lymphoblastic leukaemia (ALL)
- **Hypothyroidism**
- **Alzheimer's**
- **Atlantoaxial instability**

Down's syndrome >>>> **Endocardial cushion defects (complete atrioventricular septal canal defects)** account for about **40%** of congenital heart disease.

### Turner's syndrome

Turner's syndrome is a chromosomal disorder affecting around 1 in 2,500 females.

It is caused by either the presence of only one sex chromosome (X) or a deletion of the short arm of one of the X chromosomes.

It is denoted by **lymphocyte karyotyping** as **45, XO** or **45, X**

Features:

- Short stature
- Shield chest, widely spaced nipples
- Webbed neck
- **Bicuspid aortic valve (15%)** and **Coarctation of the aorta (5-10%)**
- **HTN:** is quite common (10%) and is typically idiopathic (essential).
- **Primary amenorrhoea.**
- Cystic hygroma (often diagnosed prenatally)
- High-arched palate
- Short fourth metacarpal
- Cubitus valgus.
- Osteoporosis
- Multiple pigmented naevi
- Lymphoedema in neonates (especially feet)



- Congenital malformations of the renal tracts.
- Increased incidence of **autoimmune** disease (especially **autoimmune Hashimoto's thyroiditis**) and **Crohn's** disease

**Hypothyroidism** is common occurring in up to **24%** of pts with Turner's S.

Turner's syndrome >> most common cardiac defect is **bicuspid aortic valve**

Turner's syndrome >>> Surveillance **echocardiography** and **renal US** are recommended.

**EX.** Young female with 1ry amenorrhea + 1 ry HTN >>>> think of: Turner syndrome or congenital adrenal hyperplasia.

### Marfan's syndrome

Marfan's syndrome is an **autosomal dominant** connective tissue disorder, so usually his parents are also very tall.

It is caused by a defect in the **fibrillin-1 gene** on chromosome 15 and affects around 1 in 3,000 people.

Unfortunately DNA testing for fibrillin gene mutations, whilst helpful, it cannot exclude the diagnosis of Marfan's because of a number of mutations exist, at least **130 mutations**.

Hence diagnosis is based on the major and minor Marfan's **features**.

Features:

- 1) Tall stature with **arm span to height ratio > 1.05** and
- 2) **Upper to lower body ratio** is **decreased** (head to symphysis pubis: symphysis pubis to toes).
- 3) High-arched palate
- 4) Arachnodactyly
- 5) **Pectus excavatum**
- 6) Pes planus
- 7) **Scoliosis** of > 20 degrees >>> Low back pain.

- 8) **Dural ectasia** (ballooning of the dural sac at the lumbosacral level): Dural ectasia affects around **60%** of patients with Marfan's syndrome. It may cause **lower back pain** associated with **neurological problems** such as **bladder** and **bowel** dysfunction like incontinence.
- 9) Heart:
- **Dilatation of the aortic sinuses (seen in 90%)** which may lead to aortic regurgitation, aortic aneurysm, aortic dissection, and
  - **Mitral valve prolapse (MVP) (75%)**: systolic murmur at mitral area.
- 10) Lungs: **repeated pneumothoraxes**
- 11) **Eyes: Upwards** lens dislocation (superotemporal ectopia lentis), blue sclera, retinal detachment and myopia.

The life expectancy of patients used to be around 40-50 years.

With the advent of **regular echocardiography monitoring** and beta-blocker/ACE-inhibitor therapy this has improved significantly over recent years.

Aortic dissection and other cardiovascular problems remain the leading cause of death however.

### **Supraventricular tachycardia (SVT)**

Whilst strictly speaking the term supraventricular tachycardia (SVT) refers to any tachycardia that is not ventricular in origin the term is generally used in the context of paroxysmal SVT.

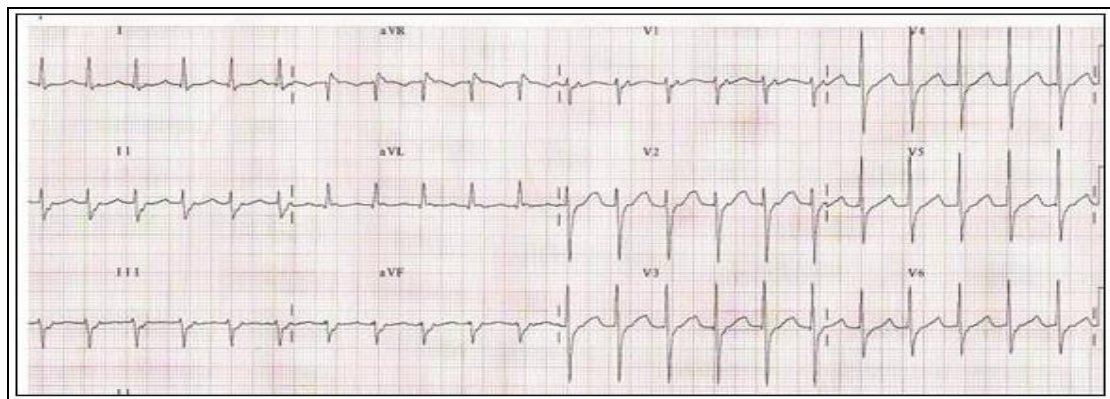
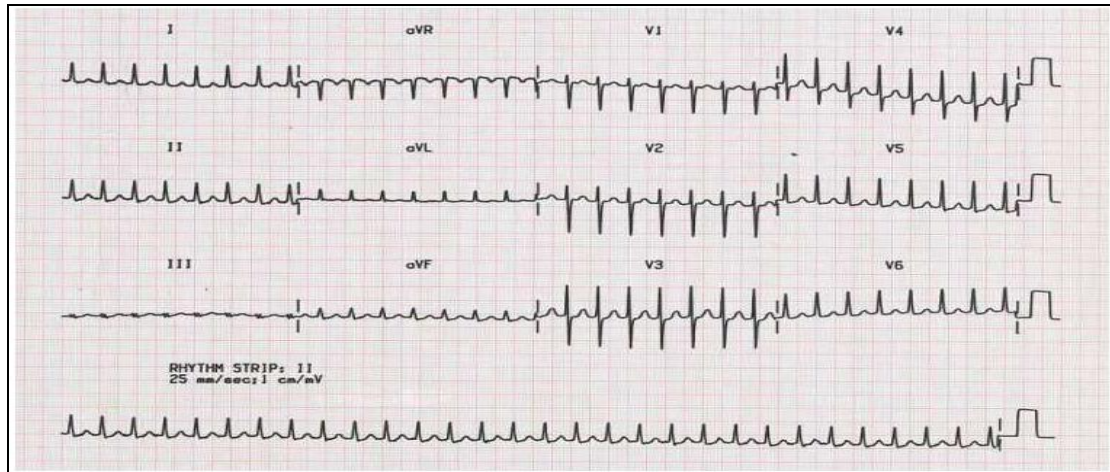
Episodes are characterised by the sudden onset of a narrow complex tachycardia, typically an atrioventricular nodal re-entry tachycardia (**AVNRT**).

Other causes include atrioventricular re-entry tachycardias (AVRT) and junctional tachycardias.

AVNRT is often seen in young patients with no previous cardiac history. Potential triggers may include exercise, emotion, alcohol, use of stimulants such as caffeine. The re-entrant circuit is formed by the creation of 2 pathways, namely the slow and fast pathways.

The fast pathway is usually situated anteriorly along septal portion of tricuspid annulus.

The slow pathway is situated posteriorly close to the coronary sinus ostium.



### Acute management (by orders):

- 1) **Vagal manoeuvres**: it is the 1<sup>st</sup> line ttt in stable patient e.g. Carotid sinus massage, Valsalva manoeuvre, ice swallowing.
- 2) **Adenosine IV**: 6mg → 12mg → 12mg (total 30 mg IV).
- 3) **DC-cardioversion** with very low energy (**50-100 J**), the patient should be sedated before cardioversion.

Adenosine is contraindicated in asthmatics >> so, **verapamil IV** or **flecainide IV** is a preferable option

### Prevention of episodes:

- Beta-blockers
- Radio-frequency ablation

Regarding the termination of acute SVT in pregnancy, **adenosine** appears to be **safe** in pregnancy.

In the case of the prevention of recurrent SVT then verapamil or beta-blockers have data supporting their use.

Current AHA/EHA criteria for the treatment of SVTs in pregnancy do suggest using **metoprolol** (level of evidence 1B) rather than verapamil (C), although they recommend avoiding the former in the first trimester.

**EX: SVT with RBBB:**

An old male with past history of IHD, he had recurrent syncopal attacks, BP 110/70 mmHg and HR 170 bpm with no signs of LVF.

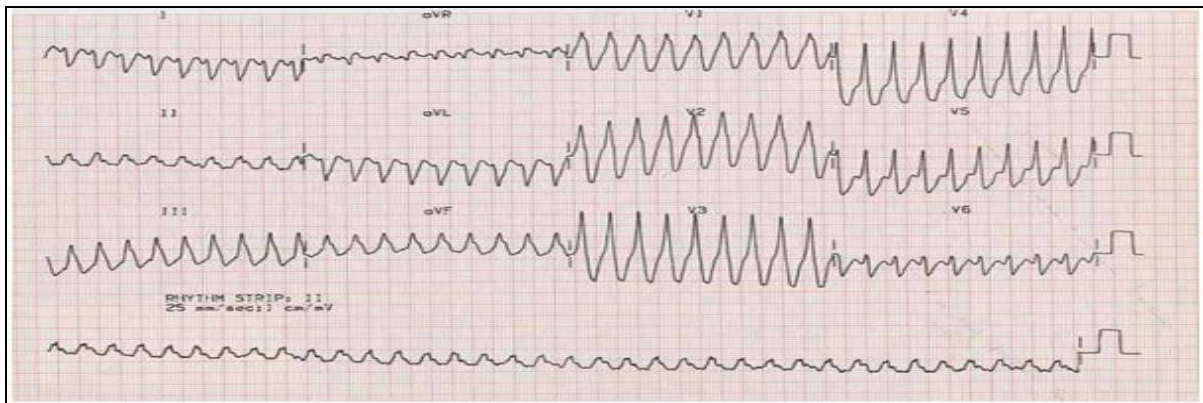
It is possible that he has been in RBBB for a significant period of time. It may be his syncopal presentation indicate a further episode of acute MI.

As he has preserved circulation so ventricular tachycardia is less likely.

Flecainide should not be used with a history of previous IHD.

Verapamil should be avoided as it can lead to a significant reduction in cardiac output.

**Synchronized DC cardioversion** is the most appropriate ttt option here.

**Adenosine**

The effects of adenosine are enhanced by dipyridamole (anti-platelet agent) and blocked by theophyllines.

**Adenosine:**

- **Dipyridamole enhances effect.**
- **Aminophylline reduces effect.**

Mechanism of action:

- Adenosine has a **very short half-life** of about **8-10 seconds**.

- Agonist of the A1 receptor which inhibits adenylyl cyclase thus **reducing cAMP** and causing hyperpolarization by **increasing outward K flux >> coronary vasodilatation** and depression of **SAN automaticity** and **AVN conduction**.
- Causes transient heart block in the AV node.

It should be given as the first line **for any narrow complex tachycardia with stable haemodynamic**.

It can be used in **broad complex tachycardia** if you are not sure is it supraventricular or a ventricular tachycardia, so consider adenosine to differentiate between SVT with aberrant conduction and VT.

Sinus tachycardia	transient atrioventricular (AV) block
Atrial fibrillation	transient AV block
Atrial flutter	transient AV block
Atrioventricular nodal re-entrant tachycardia (AVNRT)	may terminate
Atrioventricular re-entrant tachycardia (AVRT)	may terminate
Ventricular tachycardia	Likely to have no effect

Adverse effects:

- 1) Chest pain.
- 2) Bronchospasm so it should be avoided in asthmatics due to possible bronchospasm.
- 3) Can enhance conduction down accessory pathways, resulting in increased ventricular rate (e.g. WPW syndrome).

### Atrial flutter

Atrial flutter is a form of supraventricular tachycardia characterised by a succession of rapid atrial depolarisation waves.

ECG findings:

- 'sawtooth' appearance
- As the underlying atrial rate is often around 300/min the ventricular or heart rate is dependent on the degree of AV block. For example if there is 2:1 block the ventricular rate will be 150/min.
- flutter waves may be visible following carotid sinus massage or adenosine

Management:

- It is similar to that of atrial fibrillation although medication may be less effective.
- Atrial flutter is more sensitive to cardioversion however so lower energy levels may be used
- **Radiofrequency ablation of the tricuspid valve isthmus** is curative for most patients.

NB: Tachycardia with a rate of 150/min >>>>? Atrial flutter

### Multifocal atrial tachycardia (MAT)

Multifocal atrial tachycardia (MAT) may be defined as an irregular cardiac rhythm caused by at least three different sites in the atria, which may be demonstrated by morphologically distinctive P waves.

It is more common in elderly patients with chronic lung disease, for example COPD.

Management:

- Correction of hypoxia and electrolyte disturbances.
- Rate-limiting CCBs are often used first-line (Verapamil).
- Cardioversion and digoxin are not useful in the management of MAT.

### Broad complex tachycardia

Features suggesting **VT** rather than SVT with aberrant conduction:

- AV dissociation
- Fusion or capture beats
- QRS > 160 ms
- Positive QRS concordance in chest leads
- Marked left axis deviation
- History of IHD
- Lack of response to adenosine or carotid sinus massage

### Pacemakers: temporary



**Indications for a temporary pacemaker:**

- 1) Symptomatic (haemodynamically unstable) bradycardia, not responding to atropine.
- 2) Post-ANTERIOR MI:
  - Complete heart block, or
  - Type II heart block.
- 3) Trifascicular block prior to surgery.

**Indications for permanent pacemaker:**

- 1) Complete heart block (3<sup>rd</sup> degree).
- 2) Type II second degree HB even asymptomatic.
- 3) Symptomatic second degree HB.
- 4) Sinus pause of more than 3 seconds.

**NB:** Post-INFERIOR MI complete heart block is common and can be managed conservatively if asymptomatic and haemodynamically stable.

**EX:** Pt after having a **permanent pacemaker** inserted by one month >> has **fever** and **back pain**. Why?? >> Due to **Staphylococci discitis** which are skin organisms most commonly introduced during pacemaker insertion and would present with back pain.

**Pace maker nomenclature**

Pacemakers are classified by the nature of their pacing mode using a code of up to **5** letters. The NBG Pacemaker code was developed by the North American Society of Pacing and Electrophysiology (**NASPE**) and the British Pacing and Electrophysiology Group (**BPEG**):

<b>1st letter</b>	<b>2nd letter</b>	<b>3<sup>rd</sup> letter</b>	<b>4th letter</b>	<b>5th letter</b>
-------------------	-------------------	------------------------------	-------------------	-------------------

The chamber being <b>paced</b>	The chamber being <b>sensed</b>	The <b>response</b> to sensing	<b>Rate modulation</b>	<b>Multi-site pacing</b>
<b>O</b> = None <b>A</b> = Atrium <b>V</b> = Ventricle <b>D</b> = Dual (A+V) <b>S</b> = Single (A or V)	<b>O</b> = None <b>A</b> = Atrium <b>V</b> = Ventricle <b>D</b> = Dual (A+V) <b>S</b> = Single (A or V)	<b>O</b> = None <b>I</b> = Inhibited <b>T</b> = Triggered <b>D</b> = Dual (T+I)	<b>O</b> (or no letter) = None <b>R</b> = Rate modulation	<b>O</b> (or no letter) = None <b>A</b> = Atrium <b>V</b> = Ventricle <b>D</b> = Dual

The **R** in this code stands for responsive, and in an otherwise fit and well 76-year-old, he should have a responsive element to his PPM (that is, increases his heart rate with exercise).

**EX:** A gentleman is 77-years-old and has a 9 second asystolic pause causing syncope. With no breakthrough ventricular activity >>> he should therefore have a dual chamber permanent pacemaker (**DDDR**).

**NB:** A biventricular pacemaker can be indicated in heart failure patients with reduced exercise capacity, and therefore is not warranted here.

### Heart sounds

The first heart sound (S1) is caused by closure of the mitral and tricuspid valves whilst the second heart sound (S2) is due to aortic and pulmonary valve closure

#### Heart sound S1:

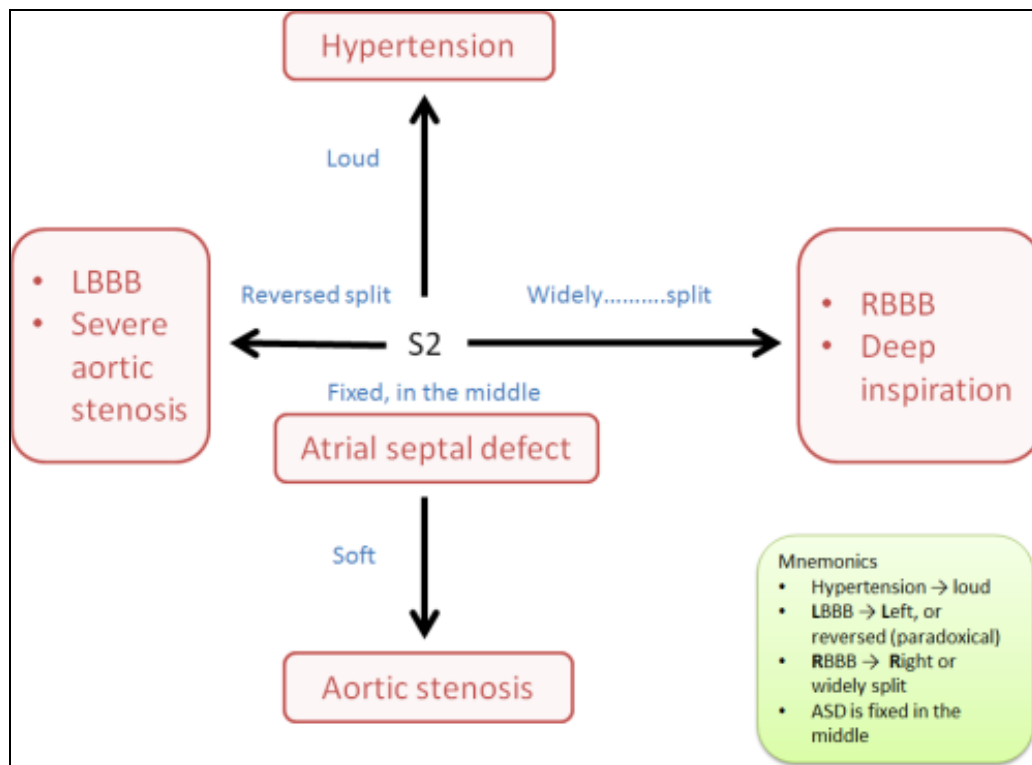
- closure of mitral and tricuspid valves
- loud in mitral stenosis
- soft if long PR or mitral regurgitation

**NB:** closure of mitral valve >>> corresponds with QRS complex in ECG.

#### Heart sound S2:

S2 is caused by the closure of the aortic valve (A2) closely followed by that of the pulmonary valve (P2)





#### Causes of a loud S2:

- **Hypertension:** **systemic** (loud A2) or **pulmonary** (loud P2)
- **Hyperdynamic** states

#### Causes of a soft S2

- **AS**

#### Causes of **fixed** split S2

- **ASD**

#### Causes of a widely split S2

- RBBB
- Deep inspiration
- Pulmonary stenosis
- Severe mitral regurgitation

Causes of a reversed (paradoxical) split S2 (P2 occurs before A2)

- LBBB
- Severe aortic stenosis
- Right ventricular pacing
- WPW type B (causes early P2)
- Patent ductus arteriosus

**Second heart sound (S2)**

- Loud: hypertension
- Soft: AS
- Fixed split: ASD
- Reversed split: LBBB

**S3 (third heart sound):**

- Caused by diastolic filling of the ventricle.
- Considered normal if < 40 years old (may persist in women up to 50 years old).
- Heard in:
  - left ventricular failure (e.g. dilated cardiomyopathy) and
  - Constrictive pericarditis (called a pericardial knock).
- NB: Gallop rhythm (S3) is an early sign of LVF.

**S4 (fourth heart sound):**

- Caused by atrial contraction against a stiff ventricle.
- May be heard in aortic stenosis, HOCM, hypertension.
- In HOCM a double apical impulse may be felt as a result of a palpable S4.

**Murmurs****Ejection systolic:**

- 1) Aortic stenosis (ejection systolic murmur radiating to the carotid area).
- 2) Pulmonary stenosis,
- 3) Fallot's (as only P2).
- 4) HOCM.
- 5) ASD.

**Holosystolic (pansystolic):**

- 1) Mitral / Tricuspid regurgitation (high-pitched and 'blowing' in character).
- 2) VSD ('harsh' in character).

If small VSD >>> systolic murmur at Left Sternal Edge (LSE)
---

**Late systolic:**

- 1) Mitral valve prolapse
- 2) Coarctation of aorta

**Early diastolic:**

- Aortic regurgitation (high-pitched and 'blowing' in character)
- Graham-Steel murmur (pulmonary regurgitation, again high-pitched and 'blowing' in character)

**Mid-late diastolic:**

- 1) Mitral stenosis ('rumbling' in character)
- 2) Austin-Flint murmur (severe aortic regurgitation, again is 'rumbling' in character)

**Continuous machine-like murmur:**

- PDA

**Most** murmurs of stenosis or regurgitation are **exaggerated** during **squatting** and get **softer** with the **Valsalva** manoeuvre. The exceptions are:

- **HOCM** where the **opposite** occurs and
- **Mitral valve prolapse** where the murmur **gets longer**.

## **Pulses**

### **Pulsus paradoxus:**

- **Greater than the normal (10 mmHg) fall** ↓ in systolic blood pressure during inspiration → **faint or absent pulse in inspiration**.
- Severe asthma, **cardiac tamponade**.

### **Slow-rising/plateau**

- Aortic stenosis

### **Collapsing:**

- Aortic regurgitation
- Patent ductus arteriosus
- Hyperkinetic (anaemia, thyrotoxic, fever, exercise/pregnancy)

### **Pulsus alternans**

- Regular alternation of the force of the arterial pulse
- Severe LVF

### **Bisferiens pulse:**

- 'Double pulse' - two systolic peaks: The first beat is the percussion wave of normal systole and the second wave is formed by recoil of the vascular bed (diastolic wave).
- Mixed aortic valve disease
- HOCM

### **'Jerky' pulse:**

- **HOCM\***

\*HOCM may occasionally be associated with a Bisferiens pulse.

### Prosthetic heart valves

The most common valves which need replacing are the aortic and mitral valve. There are 2 main options for replacement: biological (bio prosthetic) or mechanical.

Biological (bio prosthetic) (tissue) valves	Mechanical valves
<ul style="list-style-type: none"> <li>➤ Usually bovine or <b>porcine</b> in origin.</li> <li>➤ Major disadvantage is <u>structural deterioration and calcification with stenosis over time.</u></li> <li>➤ So typically must be <b><u>replaced</u></b> within 5 to <b>10</b> years.</li> <li>➤ <b><u>Older</u></b> patients (&gt; 65 years for aortic valves and &gt; 70 years for mitral valves) receive a bio prosthetic valve.</li> <li>➤ <u>Young female</u> when her desire to have children and not to take anticoagulant medication.</li> <li>➤ Long-term anticoagulation not usually needed. Warfarin may be given for the first 3 months depending on patient factors. <u>Low-dose aspirin is given long-term.</u></li> </ul>	<ul style="list-style-type: none"> <li>➤ The most common type now implanted is the <u>bileaflet</u> valve. (Ball-and-cage valves are rarely used nowadays).</li> <li>➤ Mechanical valves have a <u>low failure rate.</u></li> <li>➤ Major disadvantage is the increased risk of thrombosis <u>meaning long-term anticoagulation is needed.</u> <u>Aspirin is normally given in addition</u> unless there is a contraindication.</li> <li>➤ Target INR: <ul style="list-style-type: none"> <li>○ Aortic: 2.0-3.0</li> <li>○ Mitral: 2.5-3.5</li> </ul> </li> </ul>

#### Prosthetic heart valves >> antithrombotic therapy:

- Bioprosthetic >> Aspirin
- Mechanical >> warfarin + aspirin

Prosthetic heart valves >>> mechanical valves last longer and tend to be given to younger patients

**NB:** Following the 2008 NICE guidelines for prophylaxis of endocarditis antibiotics are no longer recommended for common procedures such as dental work.

**NB:**

If patient has prosthetic valve thrombosis (PVT) resulting in shock. This complication occurs in 0.03 to 5.5% annually with equal frequency in bioprosthesis and mechanical valves. It is more common in mitral prosthesis and with subtherapeutic anticoagulation. The best diagnostic modality is transoesophageal echocardiography; however transthoracic echocardiography is the initial choice in sick patients, and then if the diagnosis is not confirmed, a TEE can be done. Thrombolytic therapy should be given for patients in pulmonary oedema or hypotension. In stable patients, surgery is a better option for left-sided PVT, while right-sided PVT should be treated with thrombolytic agents. Serial echocardiography should be performed, and if the response is inadequate repeat thrombolytic therapy can be given.

**PVT (prosthetic valve thrombosis) with shock, hypotension or pulmonary oedema >>> Next step is Thrombolytic therapy**

**Young female patient with bicuspid aortic valve and wishes to start family >>> Biological (bio prosthetic) (porcine) valve replacement**

### Pulmonary arterial hypertension (PAH): features and management

Pulmonary arterial hypertension (PAH) may be defined as a sustained elevation in **mean** pulmonary arterial pressure of greater than 25 mmHg at rest or 30 mmHg after exercise.

PAH has recently been reclassified by the WHO into 5 groups:

#### **Group 1: Pulmonary arterial hypertension (PAH):**

- Idiopathic (IPAH) (previously termed primary pulmonary hypertension).
- Familial.
- Associated conditions: collagen vascular disease, congenital heart disease with systemic to pulmonary shunts, HIV, sickle cell disease, systemic sclerosis and drugs, toxins.
- Persistent pulmonary hypertension of the newborn.

**Group 2: Pulmonary venous hypertension with left heart disease:**

Left-sided atrial, ventricular or valvular disease such as left ventricular systolic and diastolic dysfunction, mitral stenosis, mitral regurgitation, fibrosing mediastinitis and **veno-occlusive disease**.

Pulmonary venous hypertension with increased left atrial pressure is most commonly caused by left ventricular dysfunction as in congestive cardiac failure, which causes an elevation in PA pressure by increased back-pressure through the lungs.

**Group 3: Pulmonary hypertension secondary to lung disease/hypoxia:**

- COPD
- Interstitial lung disease (ILD)
- Sleep apnoea
- High altitude

**Group 4: Pulmonary hypertension due to thromboembolic disease:**

**Group 5: Miscellaneous conditions:**

- lymphangiomatosis e.g. secondary to carcinomatosis or sarcoidosis

Features:

- **Exertional dyspnoea** is the most frequent symptom
- Chest pain and syncope may also occur
- Loud P2
- Left parasternal heave (due to right ventricular hypertrophy)

Management should first involve treating any underlying conditions, for example with anticoagulants or oxygen.

Following this, it has now been shown that **acute vasodilator testing** is central to deciding on the appropriate management strategy.

Acute vasodilator testing aims to decide which patients show a significant fall in pulmonary arterial pressure following the administration of vasodilators such as IV Epoprostenol or inhaled nitric oxide.

If there is a **positive** response to acute vasodilator testing:

- Oral calcium channel blockers.

If there is a **negative** response to acute vasodilator testing:

- **Endothelin receptor antagonists:** Bosentan and ambrisentan (They significantly reduce pulmonary artery pressure, but adverse effects include peripheral oedema and LFTs monitoring is recommended).
- Prostacyclin analogues: iloprost, treprostinil
- Phosphodiesterase- 5 (PDE-5) inhibitors: sildenafil

### **Primary Pulmonary Hypertension (PPH)**

The classification of pulmonary hypertension is currently changing with the term idiopathic pulmonary arterial hypertension (IPAH) becoming more widely used.

Primary pulmonary hypertension (PPH, now IPAH):

- Pulmonary arterial pressure ≥ 25 mmHg at rest, ≥ 30 mmHg with exercise (The normal value is 14 mmHg).
- PPH is diagnosed when no underlying cause can be found
- Around 10% of cases are familial: **autosomal dominant**
- Endothelin thought to play a key role in pathogenesis
- Associated with HIV, cocaine and anorexigens (e.g. fenfluramine).
- There is an average delay about 2 years between onset of symptoms and diagnosis by which time cor pulmonale has usually developed

Features:

- More common in females, typically presents at 20-40 years old
- Often presents in women after the birth of the first child.
- Progressive SOB
- Cyanosis
- Right ventricular heave, loud P2, raised JVP with prominent 'a' waves, tricuspid regurgitation.

Young female + increased SOB and recurrent syncope >> PPH
---

Investigation:

- 1) Echocardiography: increased right sided pressures, RV enlargement.
- 2) **V/Q scan:** may show patchy filling defects different from those seen in PE, so V/Q scan remains part of the diagnostic work up of PH.



- 3) Acute vasoreactivity test.
- 4) **Cardiac catheterisation:** ↑ PASP

**NB:** Whilst echocardiography may strongly point towards a diagnosis of pulmonary hypertension, all patients need to have right heart pressures measured.

**Cardiac catheterisation** is therefore the single most important investigation to confirm the diagnosis of pulmonary hypertension.

Management:

- Diuretics if right heart failure
- Anticoagulation
- Vasodilator therapy:
  - **Endothelin-1 receptor antagonist: Bosentan**
  - IV prostaglandins,
  - CCB, are effective in only 10-15% of patients and only recommended if there is no right sided heart failure.
- Heart-lung transplant

**NB: Pregnant females with pulmonary hypertension:**

- Have a high mortality of at least **30%** - some authors put it at **50%** - seemingly highest immediately after delivery.
- Therefore the patient **should be advised about the risk to her own health of continuing with the pregnancy versus considering a termination of pregnancy.**
- Patient who are against termination of pregnancy should be closely followed up and managed with **heparin, oxygen and pulmonary vasodilator therapy like prostacyclin.**
- **Bosentan is teratogenic and should not be used in pregnancy.**
- The patient should be advised for **contraception** in future, but oral contraceptive pills should not be used for possible increased risk of thrombo-embolism.

### Cardiac tamponade

Features:

- Dyspnoea
- Raised JVP, with an **absent Y descent** - this is due to the limited right ventricular filling

- Tachycardia
- Hypotension
- Muffled heart sounds
- Pulsus paradoxus
- Kussmaul's sign (much debate about this)
- ECG: low voltage, electrical alternans (QRS complexes with alternating amplitude).

The key differences between cardiac tamponade and constrictive pericarditis are summarised in the table below:

	Cardiac tamponade	Constrictive pericarditis
↑ JVP	NO Y descent	X + Y present
Pulsus paradoxus	Present	Absent
Kussmaul's sign	Rare	Present
Characteristic features		Pericardial calcification on CXR (dt: TB, irradiation)

A commonly used mnemonic to remember the absent Y descent in cardiac tamponade is **TAMponade = TAMpaX**

**Pulsus paradoxus** (a greater than 10 mmHg fall in systolic BP on inspiration) i.e. faint or absent pulsation during deep inspiration but this is more commonly seen in cardiac tamponade than constrictive pericarditis.

**Kussmaul's sign** (a rise in the JVP on inspiration) is more likely to be seen in constrictive pericarditis than cardiac tamponade.

Pt with dyspnoea+ distant heart sound + CXR shows a **thin rim of calcification** surrounding the cardiac outline >> **constrictive pericarditis** >> the most probable cause for this is prior **TB** infection (**tuberculous pericarditis**), **irradiation** and any cause of purulent pericarditis.

The most common cause of **constrictive pericarditis** worldwide is **tuberculous pericarditis**.

**Causes** of pericardial effusion: Neoplasia (as mesothelioma dt asbestos exposure), Infection (TB, HIV), Valvular disease (as in IEC), Trauma, Uraemia, Myxoedema.

### Restrictive cardiomyopathy

Features:

- Similar to constrictive pericarditis

Features suggesting restrictive cardiomyopathy rather than constrictive pericarditis:

- Prominent apical pulse
- Absence of pericardial calcification on CXR
- Heart may be enlarged
- ECG abnormalities e.g. bundle branch block, Q waves

Causes (5):

- 1) **Amyloidosis** (e.g. 2ry to myeloma) - most common cause in UK.
- 2) Haemochromatosis.
- 3) Sarcoidosis.
- 4) Scleroderma.
- 5) Loffler's syndrome.

Cardiac amyloidosis most commonly presents as restrictive cardiomyopathy. The clinical findings are those of right heart failure ie jugular venous distension and peripheral oedema, whereas orthopnoea and paroxysmal nocturnal dyspnoea are typically absent. In more advanced stages systolic dysfunction also occurs. Postural hypotension can occur as a result of poor ventricular filling or associated autonomic neuropathy. Combination of low-voltage electrocardiogram (ECG) and thickened ventricular walls is one of the characteristic features of cardiac amyloidosis. Other echocardiographic abnormalities include dilatation of atria, thickened interatrial septum, diastolic dysfunction and small-volume ventricles. The most distinctive feature of cardiac amyloidosis is a sparkling, granular appearance of the myocardium, but this is a relatively insensitive feature occurring only in about 25% of cases. Cardiac amyloidosis usually occurs in setting of light chain amyloidosis (AL) and hereditary amyloidosis, and rarely in secondary amyloidosis.

Haemochromatosis and sarcoidosis can also cause restrictive cardiomyopathy, but the combination of ventricular wall thickness and low-voltage ECG make the diagnosis of cardiac amyloidosis more likely. Echocardiography in ischaemic cardiomyopathy usually reveals systolic dysfunction and regional wall motion abnormalities.

Diabetic nephropathy does not explain the electrocardiographic and echocardiographic findings in this patient.

### **Dilated cardiomyopathy (DCM)**

Dilated cardiomyopathy (DCM) basics:

- Dilated heart leading to systolic (+/- diastolic) dysfunction
- All 4 chambers affected but LV more so than RV
- Features include arrhythmias, emboli, mitral regurgitation (NOT AR)
- Absence of congenital, valvular or ischaemic heart disease

Causes often considered separate entities:

- Alcohol: may improve with thiamine
- Postpartum
- Hypertension

Other causes:

- Inherited (see below)
- Infections e.g. Coxsackie B, HIV, diphtheria, parasitic
- Endocrine e.g. Hyperthyroidism
- Infiltrative e.g. Haemochromatosis, sarcoidosis (May also lead to restrictive cardiomyopathy).

- Neuromuscular e.g. Duchenne muscular dystrophy
- Nutritional e.g. Kwashiorkor, pellagra, thiamine/selenium deficiency
- Drugs e.g. Doxorubicin

Inherited dilated cardiomyopathy:

- Around a third of patients with DCM are thought to have a genetic predisposition.
- A large number of heterogeneous defects have been identified
- The majority of defects are inherited in an autosomal dominant fashion although other patterns of inheritance are seen

**NB:** Haemochromatosis is more commonly associated with restrictive cardiomyopathy but a dilated pattern may also be seen.

**NB:** There is a known association between Wilson's disease and cardiomyopathy but this is extremely rare and not often clinically significant.

**NB:** The indications of **anticoagulant** in patient with **heart failure low EF%** especially in those who have:

- 1) A previous thrombo-embolic event
- 2) Intracardiac thrombus.
- 3) LV aneurysm.

TTT of DCM: Lasix + Aldactone ± HCZ + ACEI + Carvedilol + Lanoxin + Statin + ASA ± Plavix ± Warfarin.

**NB:** RALES (Randomised Aldactone Evaluation Study) showed that **aldactone in a small dose of 25 mg** reduced mortality by **30%** when added to conventional therapy of CHF

**NB:** Patients with ICM with recurrent refractory HF although medical ttt >>> **Heart transplantation**, although **LVAD (Lt Ventricular Assisted Device)** may be used but **not currently supported in UK** due to lack of RCT evidence, there are **some interventional clinical trials have been carried out, (REMATCH trial)**, The Randomized Evaluation of Mechanical Assistance Therapy as an alternative in Congestive Heart Failure.

**ECG: axis deviation****Causes of right axis deviation (RAD):**

- right ventricular hypertrophy
- left posterior hemiblock
- chronic lung disease
- pulmonary embolism
- Ostium secundum ASD
- Wolff-Parkinson-White syndrome\* - left-sided accessory pathway
- normal in infant < 1 years old
- minor RAD in tall people

**Causes of left axis deviation (LAD):**

- LBBB
- left anterior hemiblock
- Wolff-Parkinson-White syndrome\* - right-sided accessory pathway
- hyperkalaemia
- congenital: Ostium primum ASD, tricuspid atresia
- minor LAD in obese people

\*in the majority of cases, or in a question without qualification, Wolff-Parkinson-White syndrome is associated with left axis deviation

**ECG: normal variants**

The following ECG changes are considered normal variants in an **athlete**:

- Sinus bradycardia
- First degree heart block
- Junctional rhythm
- Wenckebach phenomenon

**Cardiac catheterisation and oxygen saturation levels**

Questions regarding cardiac catheterisation and oxygen saturation levels can seem daunting at first but a few simple rules combined with logical deduction can usually produce the answer.

Let's start with the basics:

- Deoxygenated blood returns to the right side of the heart via the superior vena cava (SVC) and inferior vena cava (IVC). It has an oxygen saturation level of around **70%**. The right atrium (RA), right ventricle (RV) and pulmonary artery (PA) normally have oxygen saturation levels of around 70%
- The lungs oxygenate the blood to a level of around **98-100%**. The left atrium (LA), left ventricle (LV) and aorta should all therefore have oxygen saturation levels of 98-100%

**Some examples:**

Diagnosis & notes	RA	RV	PA	LA	LV	Aorta
<b>Normal</b>	70%	70%	70%	100%	100%	100%
<b>Atrial septal defect (ASD)</b>  The oxygenated blood in the LA mixes with the deoxygenated blood in the RA, resulting in intermediate levels of oxygenation from the RA onwards	85%	85%	85%	100%	100%	100%
<b>Ventricular septal defect (VSD)</b>  The oxygenated blood in the LV mixes with the deoxygenated blood in the RV, resulting in intermediate levels of oxygenation from the RV onwards. The RA blood remains deoxygenated	70%	85%	85%	100%	100%	100%
<b>Patent ductus arteriosus (PDA)</b>  Remember, a PDA connects the higher pressure aorta with the lower pressure PA. This results in only the PDA having intermediate oxygenation levels	70%	70%	85%	100%	100%	100%
<b>VSD with Eisenmenger's</b>	70%	70%	70%	100%	85%	85%
<b>PDA with Eisenmenger's</b>	70%	70%	70%	100%	100%	85%
<b>ASD with Eisenmenger's</b>	70%	70%	70%	85%	85%	85%

### Digoxin and digoxin toxicity

Digoxin is a cardiac glycoside now mainly used for rate control in the management of atrial fibrillation.

As it has positive inotropic properties it is sometimes used for improving symptoms (but not mortality) in patients with heart failure.

Mechanism of action:

- 1) Decreases conduction through the AVN which slows the ventricular rate in atrial fibrillation and flutter.
- 2) Stimulates vagus nerve.
- 3) Increases the force of cardiac muscle contraction due to **inhibition of the  $\text{Na}^+/\text{K}^+$  ATPase pump**.

Digoxin follows first order kinetics and has a **half-life of 1.6 days** in a patient with normal renal function.

65% of the drug absorbed remains in the system after one day.

Subsequent doses **gradually accumulate** until a **steady state concentration** is achieved after **4 to 5 days**.

Digoxin is concentrated in **tissues** and therefore **has a large apparent volume of distribution**.

Serum digoxin concentrations are **not** significantly altered by large changes in fat tissue weight so that its **distribution space correlates best with lean (that is, ideal) body weight, not total body weight**.

**Approximately 25% of digoxin in the plasma is bound to protein.**

N.B: The **half-life** of digoxin is around **36-48 hours**. This results in a **delay** before steady plasma levels are seen, so that **the full effect will not be seen for one week. So the full effect of this ttt would not be apparent for at least a week due to long half-life**.

### Digoxin toxicity:

Plasma concentration alone does not determine whether a patient has developed digoxin toxicity. The BNF advises that the likelihood of toxicity increases progressively from 1.5 to 3 mcg/l.

Features:

- Generally unwell, lethargy, nausea & vomiting, anorexia, confusion, yellow-green vision



- ECG features:
  - Down-sloping ST depression ('reverse tick')
  - Flattened/inverted T waves
  - Arrhythmias (e.g. AV block, bradycardia, PVC)
  - Prolonged PR interval
  - Short QT interval

Precipitating factors:

- Classically: **hypokalaemia** (although hyperkalaemia may also worsen digoxin toxicity, although this is very small print).
- Increasing age
- Renal failure
- Myocardial ischaemia
- Acidosis (**Hypo PH**).
- **Hypomagnesaemia**,
- **Hypoalbuminaemia**
- **Hypothermia**
- **Hypothyroidism**
- **Hypercalcaemia, Hypernatremia**
- Drugs: amiodarone, quinidine, verapamil, diltiazem, spironolactone (competes for secretion in distal convoluted tubule therefore reduce excretion), cyclosporine.
- Also drugs which cause hypokalaemia e.g. thiazides and loop diuretics.

ALL HYPO  
Except  
HYPER CA & HYPER Na

Management:

- Digi bind IV (**Digoxin specific Fab Fragment**)( **Digibind**)
- Correct arrhythmias (atropine IV in bradycardia)
- In absence of digoxin specific antibodies, insertion of a temporary pacing wire may improve the heart rate.
- Monitor K+
- If early ingestion >>> NGT and 75 gm charcoal

**Indications for administration of Digoxin specific Fab Fragment:**

- 1) Haemodynamically instability.
- 2) Life threatening arrhythmias: persistent bradycardia in spite of atropine or Tachyarrhythmia (especially ventricular).
- 3) Ingestion of > 10 mg digoxin in adults and 4 mg in children.
- 4) Plasma digoxin level > 13 nmol/L
- 5) Serum K > 5 mmol/L in acute toxicity.

**NB:**

If patient has ventricular tachycardia (VT) secondary to digoxin toxicity and is unstable haemodynamically. In the setting of digoxin toxicity DC cardioversion is not used unless all other measures have been exhausted because it is usually unsuccessful. The most useful drugs in this setting are lidocaine and phenytoin. Amiodarone and procainamide may increase digoxin levels and should be avoided.

**Digoxin toxicity with haemodynamically unstable VT >>>> the most appropriate first ttt is Phenytoin 250 mg IV over 5 min, (NOT DC Cardioversion).**

**If this Phenytoin is not effective, so Lidocaine IV may be used as next drug therapy.**

**EX: Pt with Rheumatoid Arthritis and echo finding of speckled myocardium which make the amyloidosis is the most likely underlying cause.**

**Digoxin is contraindicated in amyloid patients as patients are extremely sensitive to it. This is possible due to digoxin binding in the amyloid fibrils.**

**ECG: Prolonged PR interval**

Causes of a prolonged PR interval:

- 1) Idiopathic
- 2) Ischaemic heart disease
- 3) Digoxin toxicity
- 4) Hypokalaemia\*
- 5) Rheumatic fever
- 6) Aortic root pathology e.g. abscess secondary to endocarditis
- 7) Lyme disease
- 8) Sarcoidosis

- 1) Myotonic dystrophy (in around 20-40% of patients).
- 9) May also be seen in athletes

\*hyperkalaemia can rarely cause a prolonged PR interval, but this is a much less common association than hypokalaemia

**NB:** Hypocalcaemia >>> prolonged QT interval,

but Hypokalaemia >>> prolonged QT interval + prolonged PR interval.

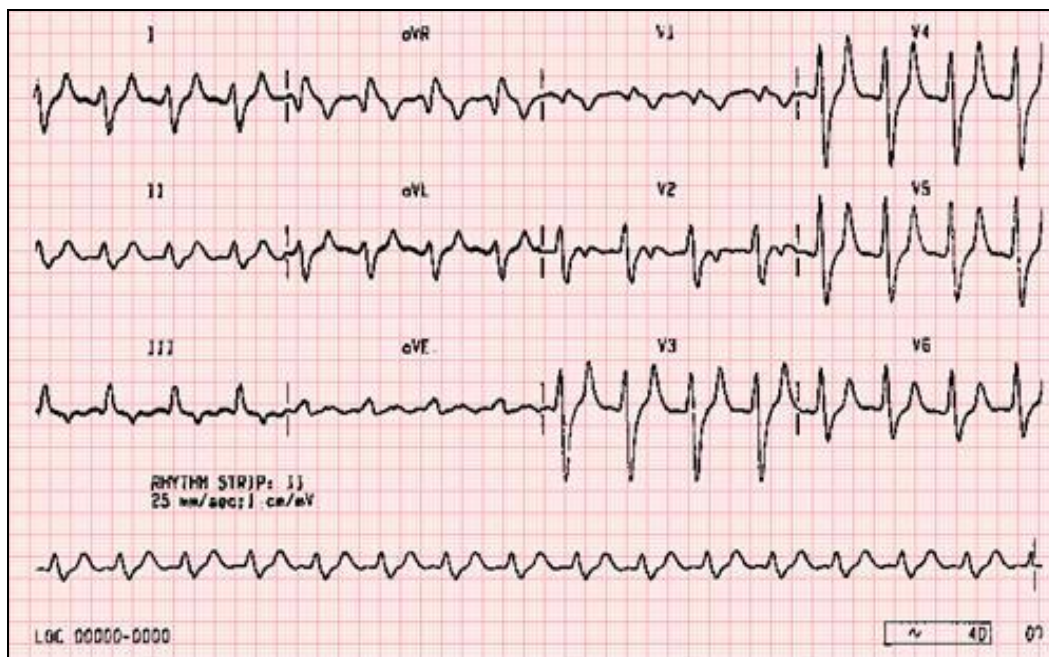
In Pt. with Infective endocarditis >>> the most important ECG change to monitor for is >>> Prolonged PR interval, which could indicate the development of an aortic abscess, an indication for surgery.

### ECG: hyperkalaemia

- 1) **Hyperacute T wave** (*They 'would hurt if you sat on them'*)
- 2) **Wide QRS complex**

The most appropriate initial therapy of hyperkalaemia is **protection of the heart** by **IV calcium gluconate** which acts within **minutes** and works by **raising** ↑ **the depolarization threshold for myocytes**.

### ECG of Hyperkalaemia:



### ECG: hypokalaemia

ECG features of hypokalaemia (serum K < 3 mmol/l):

- 1) **Prolong PR interval**
- 2) **ST depression**
- 3) Small or absent/**flat T waves** (occasionally **inversion**)
- 4) **U waves**
- 5) **Long QT**

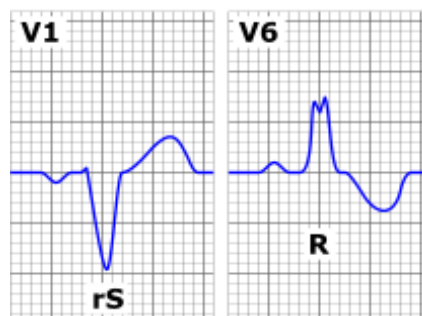
In Hypokalaemia, **U** have no Pot and no T, but a long PR and a long QT

Remember: **J** waves are seen in **hypothermia**, whilst **delta** waves are associated with **Wolff Parkinson White syndrome**.

The **causes of prominent U wave (late repolarization)**: Hypokalaemia, Cardiovascular drugs like e.g. digitalis, amiodarone, quinidine, and psychotropic drugs like e.g. phenothiazines, TCA.

### ECG: left bundle branch block (LBBB)

The diagram below shows the typical features of (LBBB):



- In LBBB there is a 'W' in V1 and a '**M**' in V6.
- In RBBB there is a '**M**' in V1 and a 'W' in V6.

One of the most common ways to remember the difference between LBBB and RBBB is **WiLLiaM MaRRoW**

Causes of LBBB:

- Ischaemic heart disease
- Cardiomyopathy
- Hypertension
- Aortic stenosis
- Idiopathic fibrosis

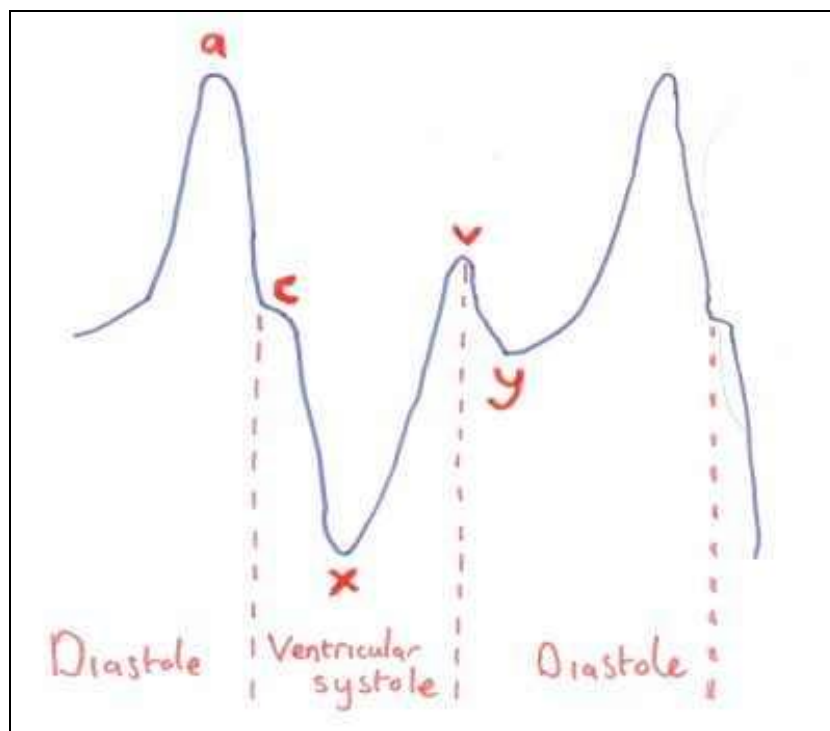
**NB:** Atrial septal defects, both primum and secundum, are associated with **RBBB** rather than LBBB.

### Jugular venous pulse (JVP)

As well as providing information on right atrial pressure, the jugular vein waveform may provide clues to underlying valvular disease.

A non-pulsatile JVP is seen in superior vena caval obstruction (SVCO).

Kussmaul's sign describes a paradoxical rise in JVP during inspiration seen in constrictive pericarditis.



**'a' wave = atrial contraction:**

- Large if atrial pressure e.g. tricuspid stenosis, pulmonary stenosis, pulmonary hypertension
- Absent if in atrial fibrillation

**Cannon 'a' waves:**

- Caused by the right atrium contracting against a closed tricuspid valve.
- Whilst tricuspid stenosis may cause large 'a' waves it does not cause cannon 'a' waves.
- Are seen in complete heart block, ventricular tachycardia/ectopics, nodal rhythm, single chamber ventricular pacing.
- May be subdivided into regular or intermittent:
  - **Regular cannon waves:**
    - VT (with 1:1 ventricular-atrial conduction).
    - Atrio-ventricular nodal re-entry tachycardia (AVNRT).
  - **Irregular cannon waves:**
    - Complete heart block.

**'c' wave:**

- closure of tricuspid valve
- not normally visible

**'v' wave:**

- Due to passive filling of blood into the atrium against a closed tricuspid valve (i.e. the venous return)
- Giant v waves in tricuspid regurgitation

**'x' descent** = fall in atrial pressure during ventricular systole

**'y' descent** = opening of tricuspid valve

**Peri-arrest rhythms: tachycardia**

The 2010 Resuscitation Council (UK) guidelines have simplified the advice given for the management of peri-arrest tachycardias.

Separate algorithms for the management of broad-complex tachycardia, narrow complex tachycardia and atrial fibrillation have been replaced by one unified treatment algorithm.

Following basic ABC assessment, patients are classified **as being stable or unstable** according to the presence of **any adverse signs**:

- 1) **Shock**: hypotension (SBP < 90 mmHg), pallor, sweating, cold, clammy extremities, confusion or impaired consciousness.
- 2) **Syncope**
- 3) **Myocardial ischaemia**
- 4) **Heart failure**

If any of the above adverse signs are present then **synchronised DC shocks** should be given.

Treatment following this is given according to whether the QRS complex is narrow or broad and whether the rhythm is regular or irregular.

The full treatment algorithm can be found at the Resuscitation Council website, below is a very limited summary:

**Broad-complex tachycardia:**

Regular:

- Assume **ventricular tachycardia** (unless previously confirmed SVT with bundle branch block) >>> loading dose of amiodarone followed by 24 hour infusion.

Irregular:

- AF with bundle branch block - treat as for narrow complex tachycardia
- Polymorphic VT (e.g. Torsade de pointes) - IV magnesium

**Narrow-complex tachycardia:**

Regular:

- Vagal manoeuvres followed by IV adenosine
- If above unsuccessful consider diagnosis of atrial flutter and control rate (e.g. Beta-blockers)

Irregular:

- Probable atrial fibrillation
- If onset < 48 hr. consider electrical or chemical cardioversion
- Rate control (e.g. Beta-blocker or digoxin) and
- Anticoagulation

#### **Peri-arrest rhythms: bradycardia**

The 2010 Resuscitation Council (UK) guidelines emphasise that the management of bradycardia depends on:

- 1) Identifying the presence of signs indicating haemodynamic compromise - 'adverse signs': see before.
- 2) Identifying the potential risk of asystole

Atropine is the first line treatment in this situation. If this fails to work, or there is the potential risk of asystole then transvenous pacing is indicated.

#### **Potential risk of asystole:**

The following indicate a potential risk of asystole and hence the need for treatment with transvenous pacing:

- Complete heart block with **broad complex** QRS
- Mobitz type II AV block
- Recent asystole
- Ventricular pause > 3 seconds

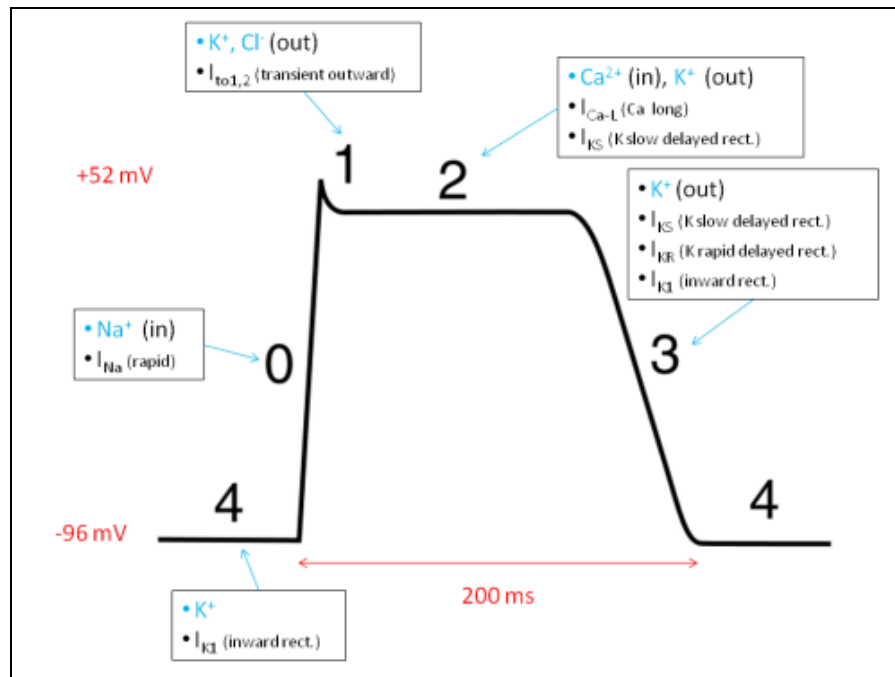
If there is a delay in the provision of transvenous pacing the following interventions may be used:

- 1) Atropine, up to maximum of 3mg
- 2) Transcutaneous pacing
- 3) Adrenaline infusion titrated to response

**NB:** Complete heart block with a narrow complex QRS complex carries the least risk of asystole as the atrioventricular junctional pacemaker may provide a haemodynamically acceptable and stable heart rate.



## Cardiac action potential



Phase	Description	Mechanism
0	Rapid depolarisation	Rapid sodium influx These channels automatically deactivate after a few ms
1	Early repolarisation	Efflux of potassium
2	<b>Plateau</b>	<b>Slow influx of calcium</b> + Efflux of potassium
3	Final repolarisation	Efflux of potassium
4	Restoration of ionic concentrations	Resting potential is restored by Na <sup>+</sup> /K <sup>+</sup> ATPase There is slow entry of Na <sup>+</sup> into the cell decreasing the potential difference until the threshold potential is reached, triggering a new action potential

**NB:** cardiac muscle remains contracted 10-15 times longer than skeletal muscle.

**Conduction velocity:**

Site	Speed
Atrial conduction	Spreads along ordinary atrial myocardial fibres at <b>1 m/sec</b>
AV node conduction	<b>0.05 m/sec</b>
Ventricular conduction	<p>Purkinje fibres are of large diameter and achieve velocities of <b>2-4 m/sec</b>.</p> <p><b>Purkinje fibres have the highest conduction velocity of all cardiac tissue types</b> (this allows a rapid and coordinated contraction of the ventricles).</p>

**Exercise: physiological changes****Blood pressure (BP):**

- **Systolic increases**,
- **Diastolic** remains the same or may decrease slightly with progressive exercise.
- leads to increased pulse pressure
- in healthy young people the increase in MABP is only slight

- With heart disease, abnormalities in BP response to exercise are common.

- A fall in BP or failure to rise or excessive rise of SDP >250 mmHg >>> is an indication to terminate the exercise test.

**Cardiac output (COP):**

- ↑ heart rate up to 3-fold increase
- ↑ stroke volume up to 1.5-fold increase
- ↑ cardiac output may be 3-5 fold
- Results from venous constriction, vasodilation and increased myocardial contractibility, as well as from the maintenance of right atrial pressure by an increase in venous return.

**The compensation mechanisms to sudden hypovolaemia include:**

- **Cardiac output (CO)** can increase, decrease, or stay the same as ( $CO = HR \times SV$ ). In the clinical scenario of open fracture of the right femur, which is bleeding profusely, it is likely that HR will increase, but **stroke volume may decrease due to the hypovolaemia**.
- **Heart rate (HR)** can **increase** due to decreased (parasympathetic) vagal stimulation and enhanced sympathetic stimulation with adrenaline.
- **Total peripheral resistance can increase** due to increased sympathetic drive. This causes peripheral vasoconstriction and preserves blood flow to essential organs, such as the brain, heart and kidneys.
- **Venous return increases** if sympathetic output increases, and this is related to the peripheral vasoconstriction. Less blood can pool in the peripheral vessels so it is transported back to the central circulation quickly. This increases venous return and maximises stroke volume.

**ECG: hypothermia**

The following ECG changes may be seen in hypothermia:

- Bradycardia
- First degree heart block
- **'J' wave** - small positive deflection hump at the end of the QRS complex, it is highly **sensitive** and **specific** for hypothermia.
- Long QT interval
- Atrial and ventricular arrhythmias

**ECG: ST elevation**

Causes of ST elevation:

- 1) Myocardial infarction
- 2) Pericarditis
- 3) Left ventricular aneurysm post MI
- 4) Prinzmetal's angina (coronary artery spasm)
- 5) **Normal variant - 'high take-off' "early repolarization"**
- 6) Rare: subarachnoid haemorrhage, part of spectrum of changes in hyperkalaemia

**ECG: ST depression**

Causes of ST depression:

- Secondary to abnormal QRS (LVH, LBBB, RBBB)
- Ischaemia
- Syndrome X
- Digoxin
- Hypokalaemia

**Mitral valve prolapse (MVP)**

Mitral valve prolapse is common, occurring in around 5-10 % of the population and it is more common in females.

It is usually idiopathic but may be associated with a wide variety of cardiovascular disease and other conditions

Associations:

- congenital heart disease: PDA, ASD
- cardiomyopathy
- Turner's syndrome
- Marfan's syndrome, Fragile X
- Osteogenesis imperfecta
- Pseudoxanthoma elasticum
- Wolff-Parkinson White syndrome
- Long-QT syndrome
- Ehlers-Danlos Syndrome
- Polycystic kidney disease

Features:

- Patients may complain of atypical chest pain or palpitations
- Mid-systolic click (occurs later if patient squatting)
- Late systolic murmur (longer if patient standing)
- Complications: mitral regurgitation, arrhythmias (including long QT), emboli, sudden death

TTT:

- Mild to moderate >>> **Bisoprolol** and **follow** up echo every 2-3 years.
- Severe with LV dysfunction >>> **MVR**.
- Endocarditis prophylaxis is not required according to NICE guidelines.

**NB:** In acromegaly (it is NOT a common association).

### **Adult advanced life support**

The joint European Resuscitation Council and Resuscitation Council (UK) 2010 guidelines do not alter significantly from the 2005 guidelines. Please see the link for more details, below is only a very brief summary of key points / changes.

Major points include:

- The 2010 guidelines do not support the concept of 'checking for circulation': **absence of breathing**, in a non-responsive individual, is now used as the main sign of cardiac arrest and so >>>immediate start chest compression 30:2.
- In reality most medical professionals will check for a carotid pulse whilst assessing breathing, but in this scenario to wait a further 10 seconds before starting chest compressions is not justifiable.
- Ratio of chest compressions to ventilation is **30:2**.
- Chest compressions are now continued while a defibrillator is charged.
- During a VF/VT cardiac arrest, **adrenaline 1 mg is given once chest compressions have restarted after the third shock and then every 3-5 minutes** (during alternate cycles of CPR). In the 2005 guidelines, adrenaline was given just before the third shock. Amiodarone 300 mg is also given after the third shock.
- Atropine is no longer recommended for routine use in asystole or pulseless electrical activity (PEA).
- A single shock for VF/pulseless VT followed by 2 minutes of CPR, rather than a series of 3 shocks followed by 1 minute of CPR.
- Asystole/pulseless-electrical activity should be treated with 2 minutes of CPR, rather than 3, prior to reassessment of the rhythm.
- Delivery of drugs via a tracheal tube is no longer recommended.
- Following successful resuscitation oxygen should be titrated to achieve saturations of 94-98%. This is to address the potential harm caused by hyperoxaemia.

## Atrial myxoma

### Overview:

- 75% occur in left atrium.
- More common in females.

### Features:

- It is the most common primary heart tumour.
- It produces symptoms either through distant embolisation or mechanical interference with cardiac function.
- One third present with emboli, a third with systemic inflammation (ESR elevated in 1/3) and a third are asymptomatic when detected.
- Systemic: exertional dyspnoea in 75%, fatigue, weight loss, fever, clubbing, dizziness, syncope (dt obstruction of mitral valve), and sudden cardiac death in 15%.
- Emboli.
- Atrial fibrillation.
- Loud S1 due to delay in mitral valve closure due to prolapse of the tumour into the mitral valve orifice.
- Mid-diastolic murmur, 'tumour **plop**' (↑ with sitting forward).
- Echo: pedunculated heterogeneous mass typically attached to the fossa ovalis region of the interatrial septum.
- CXR: intra-cardiac calcification

Carney's complex is a familial multiple neoplasia and lentiginosis syndrome, associated with

- **Primary adrenal hypercortisolism**
- Lentigines and naevi of the skin
- Various tumours including myxoma.

Although rare (2 per 100 000 with a female to male ratio of 2:1) the diagnosis of atrial myxoma should be entertained in a person who presents with finger clubbing, normocytic anaemia, a positional murmur and intracardiac calcification in the chest X-ray. The history of fainting spells suggests transient left ventricular inflow obstruction. The patient should undergo urgent echocardiography and be referred for surgery if the diagnosis of myxoma is confirmed, as complete removal is curative.

**Cardiac imaging: non-invasive techniques excluding echocardiography**

The ability to image the heart using non-invasive techniques such as MRI, CT and radionuclides has evolved rapidly over recent years.

**Nuclear imaging:**

These techniques use radiotracers which are extracted by normal myocardium. Examples include:

- Thallium
- Technetium (99mTc) SestaMIBI: a coordination complex of the radioisotope technetium-99m with the ligand methoxyisobutyl isonitrile (MIBI), used in 'MIBI' or cardiac Single Photon Emission Computed Tomography (SPECT) scans
- Fluorodeoxyglucose (FDG): used in Positron Emission Tomography (**PET**) scans

The primary role of SPECT is to assess myocardial perfusion and myocardial viability.

Two sets of images are usually acquired. First the myocardium at rest followed by images of the myocardium during stress (either exercise or following adenosine / dipyridamole).

By comparing the rest with stress images any areas of ischaemia can be classified as reversible or fixed (e.g. following a myocardial infarction).

Cardiac PET is predominately a research tool at the current time.

**MUGA:**

- Multi Gated Acquisition Scan, also known as radionuclide angiography
- Radionuclide (technetium-99m) is injected IV.
- The patient is placed under a gamma camera
- May be performed as a stress test
- It can accurately measure left ventricular ejection fraction (LVEF). **Typically used before and after cardiotoxic drugs are used in cancer patients.**

**Cardiac Computed Tomography (CT):**

Cardiac CT is useful for assessing suspected ischaemic heart disease, using two main methods:

- Calcium score: there is known to be a correlation between the amount of atherosclerotic plaque calcium and the risk of future ischaemic events. Cardiac CT scan quantifies the amount of calcium producing a 'calcium score'.
- Contrast enhanced CT: allows visualisation of the coronary artery lumen.

If these two techniques are combined cardiac CT has a very high negative predictive value for ischaemic heart disease.

### **Cardiac MRI:**

Cardiac MRI (commonly termed CMR) has become the gold standard for providing structural images of the heart. It is particularly useful when assessing congenital heart disease, determining right and left ventricular mass and differentiating forms of cardiomyopathy. Myocardial perfusion can also be assessed following the administration of gadolinium. Currently CMR provides limited data on the extent of coronary artery disease.

### **Implantable cardioverter defibrillators (ICD) (Dual chamber pacemaker)**

Indications:

- 1) Long QT syndrome (LQTS)
- 2) Hypertrophic obstructive cardiomyopathy (HOCM)
- 3) (ARVC) arrhythmogenic right ventricular cardiomyopathy causing cardiac arrest.
- 4) Brugada syndrome
- 5) **Cardiac arrest due to VT/VF.**
- 6) **Sustained VT** causing haemodynamic compromise.
- 7) **Non-sustained VT** on 24 hr. monitoring with prior **MI**.
- 8) Unexplained syncope with VT inducible at EPS.
- 9) Inducible VT on EPS and ejection fraction < 35%.
- 10) Chronic heart failure, left ventricular ejection fraction (LVEF) less than 40% and associated syncope episodes due to non-sustained VT post-MI, non-sustained VT with LVEF less than 40%.
- 11) Following repair of tetralogy of Fallot.
- 12) SSS (sick sinus syndrome)

Patients with heart failure are at increased risk of SCD from ventricular arrhythmias. So ICD is indicated for **primary prevention of SCD** in patients who have history of **prior MI** and **all of the following**:



- 1) Non-sustained VT.
- 2) Inducible arrhythmia on EPS.
- 3) LV EF less than 35% and no worse than NYHA class III.

So that all these patients should be **evaluated by EPS** and if **inducible arrhythmias** are documented, an **ICD** should be placed.

Some trials like MADIT II have also found that ICD implantation in such patients even without EPS also leads to reduction in mortality, although guidelines are yet to completely reflect this information.

## **Syncope**

Syncope may be defined as a transient loss of consciousness due to global cerebral hypoperfusion with rapid onset, short duration and spontaneous complete recovery. Note how this definition excludes other causes of collapse such as epilepsy.

The European Society of Cardiology published guidelines in 2009 on the investigation and management of syncope. They suggested the following three classification:

### **1) Reflex syncope (neurally mediated):**

- Vasovagal: triggered by emotion, pain or stress. Often referred to as 'fainting'
- Situational: cough, micturition, gastrointestinal
- Carotid sinus hypersensitivity (CSH)

This patient has carotid sinus hypersensitivity (CSH), demonstrating an exaggerated response to carotid sinus stimulation. The diagnosis is only made after ischaemic heart disease or rhythm disturbance have been reasonably excluded, as in this case. CSH may be predominantly cardioinhibitory (resulting in bradycardia), vasodilatory (resulting in hypotension), or a mixture of the two. Cardioinhibitory CSH is usually managed with insertion of a dual-chamber pacemaker, and vasodilatory CSH is managed with support stockings, fludrocortisone and midodrine (available on a named-patient basis in the UK).

### **2) Orthostatic syncope:**

- Primary autonomic failure: Parkinson's disease, Lewy body dementia
- Secondary autonomic failure: e.g. Diabetic neuropathy, amyloidosis, uraemia
- Drug-induced: diuretics, alcohol, vasodilators
- Volume depletion: haemorrhage, diarrhoea

### **3) Cardiac syncope:**

- Arrhythmias: bradycardias (sinus node dysfunction, AV conduction disorders) or tachycardias (supraventricular, ventricular).
- Structural: valvular, myocardial infarction, hypertrophic obstructive cardiomyopathy.
- Others: pulmonary embolism.

Reflex syncope is the most common cause in all age groups although orthostatic and cardiac causes become progressively more common in older patients.

Evaluation:

- Cardiovascular examination
- Postural blood pressure readings: a symptomatic fall in systolic BP > 20 mmHg or diastolic BP > 10 mmHg or decrease in systolic BP < 90 mmHg is considered diagnostic.
- ECG, 24 hour ECG
- Carotid sinus massage
- Tilt table test

### **Pulmonary capillary wedge pressure (PCWP)**

PCWP is measured using a balloon tipped **Swan-Ganz catheter** which is inserted into the **pulmonary artery**. The pressure measured is similar to that of the **left atrium (normally 6-12 mmHg)**.

One of the main uses of measuring the PCWP is **determining whether pulmonary oedema is caused by either heart failure or acute respiratory distress syndrome (ARDS)**.

In many modern ITU departments PCWP measurement has been replaced by non-invasive techniques.

**APO >> Swan-Ganz catheter >> PCWP >> equal to LA pressure.** (N= 6-12 mmHg)

**N.B:** The normal pulmonary circulation is characterised by >> **low pressures, low flow rates, high compliance** vessels than that of the systemic circulation

**Cardiac transplantation**

By **5** years following cardiac transplantation >>> nearly **all** patients have some degree of **Coronary arteriopathy (small coronary vascular narrowing)** >>> fatigue with exercise, pedal oedema, Bibasilar crackles and orthopnoea.

**Bradycardia** and **syncope** in patient with **cardiac transplant** >>> the pharmacotherapy of bradycardias is different for this group of patients. This is because the transplanted heart is denervated.

Therefore there is **no place for atropine, even at higher doses**, hence repeated doses of atropine at 500 mcg per dose or at 1 mg per dose are incorrect, The Resuscitation Council (UK) guidelines suggest using **theophylline IV** as a slow intravenous infusion (100-200 mg).

**NB:**

Becker muscular dystrophy is an X-linked genetic disorder resulting from a mutation in the dystrophin gene. The clinical picture is similar to that of Duchenne's muscular dystrophy but it is much milder. Patients usually present between the ages of 5 and 15 years, though presentation may not be until the fourth or fifth decade. Patients may present with heart failure secondary to dilated cardiomyopathy instead of the classic proximal muscle weakness. Inheritance is X-linked recessive.

**NB:****Tocolysis-associated pulmonary oedema:**

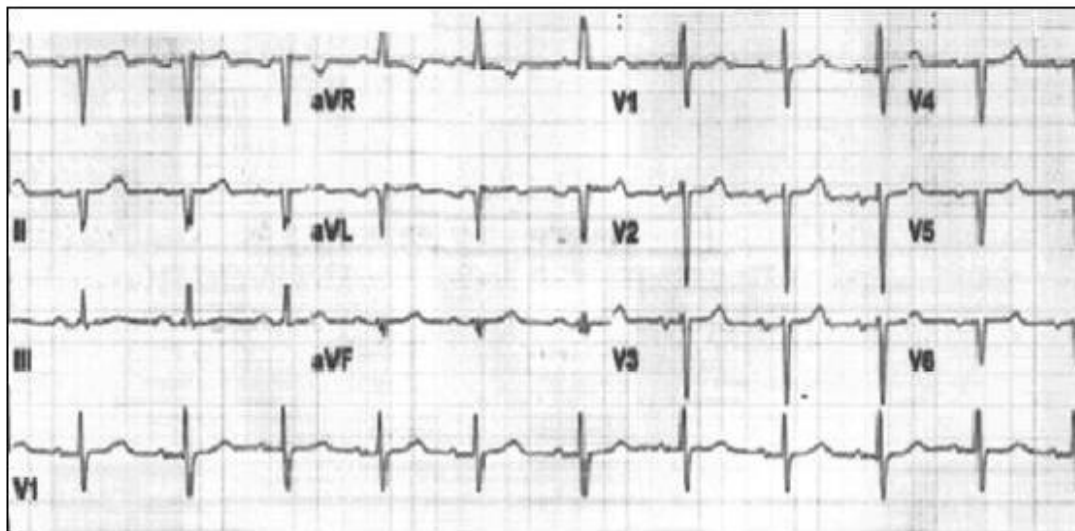
Tocolytics are medications administered for the suppression of premature contractions. Acute pulmonary oedema can occur with administration of  $\beta_2$  agonists for tocolysis in up to 5–15% of cases. It usually occurs after 24 h of administration of these agents. The chest X-ray reveals pulmonary infiltrates and normal heart size. Concomitant use of corticosteroids that are often administered for lung maturation have also been implicated as risk factor for development of tocolysis-associated pulmonary oedema. Treatment involves stopping the tocolytics, oxygen and careful volume control. Peripartum cardiomyopathy and myocarditis cause systolic dysfunction and will be expected to show cardiomegaly on chest X-ray. Pulmonary embolism is unlikely to cause bilateral chest infiltrates. As the patient's examination was normal prior to this event, mitral stenosis is less likely.

**EX:** pregnant female admitted in hospital with premature labour and received tocolysis IV then developed acute dyspnoea >>>> **Tocolysis-associated pulmonary oedema**

## Dextrocardia

**Dextrocardia** >>> characteristic **ECG** features are:

- 1) Inverted P waves with negative QRS deflection in **lead I**,
- 2) Upright P waves with a positive QRS deflection in lead **aVR** with mirror image finding in lead **aVL**.
- 3) A shift of the P axis (usually about + 120 degrees) and
- 4) Reversed R wave progression through chest leads V1 to V6.



Dextrocardia may be associated with **Kartagener's** syndrome which is dextrocardia + bronchiectasis + chronic sinusitis + immotile cilia infertility.

Dextrocardia may be alone or associated with **situs inversus totalis**, so should do both CXR and abdomen US.

**SSS (Sick Sinus Syndrome) = Sinus Node Disease (SND) = (tachy-brady syndrome)**

Usually occurs in old patients with attacks of symptomatic bradycardia with dizziness, syncope and headedness.

Also this sinus bradycardia may be associated with episodes of AF.

Also may be associated with sinus pause (sinus arrest), up to 2 seconds may be accepted.

**TTT: Dual chamber pacemaker.**

If patient only has a VVI pacemaker in situ, it will prevent bradycardia-induced syncope but may be presented with symptomatic fast AF.

If patient develops rapid AF >>> ttt is initially to cardiovert this patient then the pacemaker function and settings should be rechecked after cardioversion, subsequently the patient should be treated with antiarrhythmic medication to prevent recurrences of fast AF.

DC cardioversion is not contraindicated in patients with pacemakers.

If patient is on long time high dose of beta blocker, so gradual withdrawal of  $\beta$ B to avoid rebound tachycardia.

### **Fabry disease**

Fabry disease is an **X linked recessive** condition due to a deficiency of the enzyme alpha-galactosidase A which results in the accumulation of a glycolipid within the endothelium resulting in abnormalities of the skin, eye, kidneys and neurological systems.

The responsible gene is located on the long arm of the X chromosome.

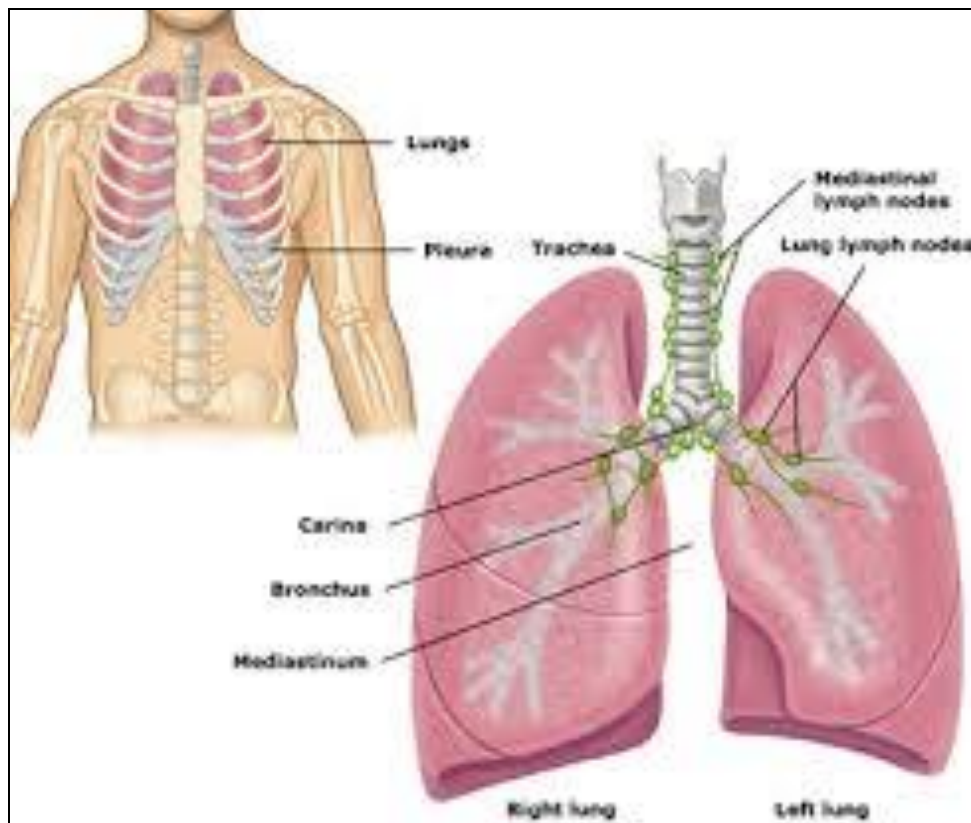
The diagnosis is confirmed by demonstration of **absent or deficient levels of alpha-galactosidase A** in leucocytes, plasma or cultured fibroblasts.

An X linked recessively inherited condition can exist in **female carriers** who may exhibit mild to moderate symptoms. This is due to variable expression according to random X inactivation of the affected gene in embryogenesis and explains the presence of mild disease in this patient's sister.

The disorder has three distinct clinical entities:

- 1) Classical presentation in the male homozygote with early presentation in childhood - angiokeratomas, heart failure, cataracts and renal disease.
- 2) Male homozygotes with atypical presentation in adulthood with proteinuria, acroparaesthesia, angiokeratomas and cardiomegaly.
- 3) Female heterozygotes can present again in adulthood with similar mild symptoms.

# Pulmonology



**Respiratory physiology: lung volumes****Tidal volume (TV):**

- Volume inspired or expired with each breath at rest
- 500ml in males, 350ml in females

**Inspiratory reserve volume (IRV) = 2-3 L:**

- Maximum volume of air that can be **inspired** at the end of a normal tidal inspiration
- Inspiratory capacity = TV + IRV

**Expiratory reserve volume (ERV) = 750ml:**

- Maximum volume of air that can be **expired** at the end of a normal tidal expiration

**Residual volume (RV) = 1.2L:**

- Volume of air remaining after maximal expiration
- Increases with age
- $RV = FRC - ERV$

**Vital capacity (VC) = 5L:**

- **Maximum volume of air that can be expired after a maximal inspiration**
- **4,500 ml in males and 3,500 ml in females**
- Decreases with age
- $VC = \text{inspiratory capacity} + ERV$

**Total lung capacity (TLC):** is the sum of the vital capacity + residual volume

**Physiological dead space ( $V_D$ ):**

- $V_D = \text{tidal volume} * (PaCO_2 - PeCO_2) / PaCO_2$
- where  $PeCO_2$  = expired air  $CO_2$



## Oxygen dissociation curve

The oxygen dissociation curve describes the relationship between the **percentage of saturated haemoglobin** and **partial pressure of oxygen** in the blood. It is **not affected by haemoglobin concentration**.

Basics:

- Shifts to right = for given oxygen tension there is reduced saturation of Hb with oxygen i.e. enhanced oxygen delivery to tissues.
- Shifts to left = for given oxygen tension there is increased saturation of Hb with oxygen i.e. decreased oxygen delivery to tissues

Shifts to <u>L</u> eft = <u>L</u> ower oxygen delivery	Shifts to <u>R</u> ight = <u>R</u> aised oxygen delivery
HbF, Methaemoglobin, Carboxyhaemoglobin <u>L</u> ow [H <sup>+</sup> ] (alkali) <u>L</u> ow PCO <sub>2</sub> <u>L</u> ow 2,3-DPG <u>L</u> ow temperature	Raised [H <sup>+</sup> ] (acidic) Raised PCO <sub>2</sub> Raised 2,3-DPG* Raised temperature

### Oxygen dissociation curve:

- Shifts **Left** - **Lower** oxygen delivery - Lower acidity, temp, PCO<sub>2</sub>, 2-3 DPG - also HbF, carboxy/methaemoglobin.
- Shifts **Right** - **Raised** oxygen delivery - **Raised** acidity, temp, PCO<sub>2</sub>, 2-3 DPG

The **L** rule

Shifts to **L** → **Lower** oxygen delivery, caused by:

- **L**ow [H<sup>+</sup>] (alkali)
- **L**ow pCO<sub>2</sub>
- **L**ow 2,3-DPG (2,3-diphosphoglycerate)
- **L**ow temperature

Another mnemonic is '**CADET**, face **Right!**' for **CO**<sub>2</sub>, **A**cid, 2,3-**D**PG, **E**xercise and **T**emperature.



**Respiratory physiology: control**

Control of respiration:

- 1) **Central** regulatory centres at pons and medulla
- 2) Central and peripheral **chemoreceptors**
- 3) **Pulmonary** receptors

**1) Central regulatory centres at pons and medulla:**

- 1) Apneustic centre (lower pons).
- 2) Pneumotaxic centre (upper pons).
- 3) Medullary respiratory centre.

**2) Central and peripheral chemoreceptors:**

- 1) Central: **raised [H<sup>+</sup>]** in **ECF** >>> **stimulates respiration**.
- 2) Peripheral: **carotid + aortic bodies**, respond to raised pCO<sub>2</sub> & [H<sup>+</sup>], lesser extent low pO<sub>2</sub>.

**3) Pulmonary receptors:**

- 1) **Stretch** receptors, lung **distension** causes **slowing** of respiratory rate (**Hering-Bruer reflex**).
- 2) Irritant receptor, leading to bronchoconstriction.
- 3) Juxtacapillary receptors, stimulated by stretching of the microvasculature.

**Respiratory physiology****Chloride shift:**

- CO<sub>2</sub> diffuses into RBCs
- CO<sub>2</sub> + H<sub>2</sub>O ---- carbonic anhydrase → HCO<sub>3</sub><sup>-</sup> + H<sup>+</sup>
- H<sup>+</sup> combines with Hb
- HCO<sub>3</sub><sup>-</sup> diffuses out of cell, - Cl<sup>-</sup> replaces it

**Bohr Effect:**

- Increasing **acidity** (or **PCO<sub>2</sub>**) means **O<sub>2</sub> binds less well to Hb**.

**Haldane effect:**

- Increase **PO<sub>2</sub>** means **CO<sub>2</sub> binds less well to Hb**.

**Respiratory physiology: hypoxia**

A fall in the partial pressure of oxygen in the blood leads to **vasoconstriction** of the **pulmonary** arteries.

This allows blood to be diverted to better aerated areas of the lung and improves the efficiency of gaseous exchange.

The **pulmonary arteries** (NOT the skin arteries) is the **first** type of blood vessel to **vasoconstrict** in the presence of **hypoxia**.

**Respiratory physiology: lung compliance (C=V/P)**

Lung compliance is defined as change in lung **volume** per unit change in airway **pressure**.

Causes of increased compliance:	Causes of decreased compliance:
<ul style="list-style-type: none"> <li>• <b>Age</b></li> <li>• <b>Emphysema</b> - this is due to loss alveolar walls and associated elastic tissue</li> </ul>	<ul style="list-style-type: none"> <li>• Pulmonary <b>oedema</b></li> <li>• Pulmonary <b>fibrosis</b></li> <li>• <b>Pneumectomy</b></li> <li>• <b>Kyphosis</b></li> </ul>

The **pathophysiological** changes which is most responsible for **emphysema** is **Destruction of alveolar walls secondary to proteinases**.

Proteinases such as **elastase** cause **irreversible** damage to the supporting connective tissue of the alveolar septa. Smoking accelerates this process.

**Asthma: diagnosis in adults**

- The 2008 British Thoracic Society (BTS) guidelines marked a subtle change in the approach to diagnosing asthma.
- This approach is supported in the updated 2011 guidelines. It suggests dividing patients into a high, intermediate and low **probability** of having asthma based on the presence or absence of typical symptoms.
- The new BTS guidelines take a more practical approach to diagnosing asthma.
- If a patient has typical symptoms of asthma a trial of treatment is recommended.
- Normal spirometry when the patient is well does not exclude a diagnosis of asthma.

Asthma diagnosis >>> if high probability of asthma >>> start treatment

Example of features used to assess asthma:

Increase possibility of asthma	Decrease possibility of asthma
<ul style="list-style-type: none"> <li>➤ <u>Wheeze</u> breathlessness, chest <u>tightness</u> and cough, worse at night/early morning.</li> <li>➤ <u>Nocturnal</u> cough or wheeze</li> <li>➤ Symptoms after exercise</li> <li>➤ Allergen exposure</li> <li>➤ Beta blockers or aspirin.</li> <li>➤ History of <u>atopic</u> disorder. (<u>Eczema</u>) in family.</li> <li>➤ Wheeze heard on auscultation.</li> <li>➤ Unexplained peripheral blood <u>eosinophilia</u>.</li> </ul>	<ul style="list-style-type: none"> <li>➤ Prominent dizziness, light-headedness, peripheral <u>tingling</u>.</li> <li>➤ Chronic productive cough in the absence of wheeze or breathlessness.</li> <li>➤ Repeatedly normal physical examination.</li> <li>➤ Significant smoking history (i.e. &gt; 20 pack-years).</li> <li>➤ Normal PEF or Spirometry when symptomatic.</li> </ul>

Management is based on this assessment:

- High probability: trial of treatment
- Low probability: investigate/treat other condition
- Intermediate probability: see below

For patients with an intermediate probability of asthma further investigations are suggested.

The guidelines state that Spirometry is the preferred initial test:

- FEV1/FVC < **0.7**: trial of treatment
- FEV1/FVC > 0.7: further investigation/consider referral

Recent studies have shown the limited value of other 'objective' tests. It is now recognised that in patients with normal or near-normal pre-treatment lung function there is little room for measurable improvement in FEV1 or peak flow.

A > 400 ml improvement in FEV1 is considered significant

- before and after 400 mcg inhaled salbutamol in patients with diagnostic uncertainty and airflow obstruction present at the time of assessment
- if there is an incomplete response to inhaled salbutamol, after either inhaled corticosteroids (200 mcg twice daily beclometasone equivalent for 6-8 weeks) or oral prednisolone (30 mg once daily for 14 days)

It is now advised to interpret peak flow variability with caution due to the poor sensitivity of the test

- Diurnal variation % = [(Highest - Lowest PEFR) / Highest PEFR] x 100
- Assessment should be made over 2 weeks
- Greater than 20% diurnal variation is considered significant

**Diurnal variation** of peak expiratory flow rate (**PEFR**) **greater than 20%** is one of the diagnostic criteria for asthma.

IgE being elevated is non-specific, but can suggest an atopic phenotype.

Skin prick tests can confirm allergy, but this does not necessarily mean the patient will develop asthma.

**Stepwise management of stable asthma in adults (a step-wise approach):**

Step	Management
<b>Step 1</b>	Inhaled <b>short-acting B2 agonist</b> (SABA) PRN (e.g. salbutamol PRN)
<b>Step 2</b>	<ul style="list-style-type: none"> <li>➤ Add <b>Inhaled Corticosteroid (ICS)</b> at 200-800 mcg/day (beclometasone dipropionate or <u>fluticasone</u>).</li> <li>➤ 400 mcg is an appropriate starting dose for many patients.</li> <li>➤ Start at dose of inhaled steroid appropriate to severity of disease.</li> </ul>
<b>Step 3</b>	1. Add <b>inhaled long-acting B2 agonist (LABA)</b> : (e.g. <u>Salmeterol</u> 50mg/d or formoterol) 2. Assess control of asthma: <ul style="list-style-type: none"> <li>• <b>Good</b> response to LABA &gt;&gt;&gt; continue LABA</li> <li>• <b>Partial</b> response i.e. benefit from LABA but <u>control still inadequate</u> &gt;&gt;&gt; continue LABA and increase ICS dose to 800 mcg/day (if not already on this dose).</li> <li>• <b>No</b> response to LABA &gt;&gt;&gt; stop LABA + increase ICS inhaled steroid to 800 mcg/ day + institute trial of other therapies, leukotriene receptor antagonist or SR theophylline.</li> </ul>
<b>Step 4</b>	Consider trials of: <ul style="list-style-type: none"> <li>• <u>Increasing inhaled steroid</u> up to 2000 mcg/day</li> <li>• Addition of <u>a fourth drug</u> e.g. Leukotriene receptor antagonist, SR theophylline, B2 agonist tablet.</li> </ul>
<b>Step 5</b>	<ul style="list-style-type: none"> <li>➤ Use <b>daily steroid tablet</b> in lowest dose providing adequate control.</li> <li>➤ Consider other treatments to minimise the use of steroid tablets.</li> <li>➤ <u>Maintain high dose inhaled steroid at 2000 mcg/day.</u></li> <li>➤ Refer patient for specialist care.</li> </ul>

**Additional notes:****Leukotriene receptor antagonists:**

- e.g. **Montelukast, zafirlukast**
- Have **both** anti-inflammatory and bronchodilatory properties.
- Should be used when patients are poorly controlled on high-dose inhaled corticosteroids (ICS) and a long-acting b2-agonist (LABA).
- Particularly useful in aspirin-induced asthma.
- Associated with development / worsening of Churg-Strauss syndrome.

\* Fluticasone is more lipophilic and has a longer duration of action than beclometasone also it is roughly twice as potent as beclometasone.

\* Hydrofluoroalkane is now replacing chlorofluorocarbon as the propellant of choice. Only half the usually dose is needed with hydrofluoroalkane due to the smaller size of the particles.

\* (LABA) Long acting B2-agonists acts as bronchodilators but also inhibit mediator release from mast cells. Recent meta-analysis showed adding salmeterol improved symptoms compared to doubling the inhaled steroid dose.

\* **Salmeterol** has been reported to produce **an acute exacerbation of asthma**, possibly through **an acute hypersensitivity reaction** ☹

\* **Seretide Discus®** = Salmeterol 50 mg+ Fluticasone 250 or 500 Mcg

- Both the British National Formula (BNF) and British Thoracic Society (BTS) guidelines stress the need for good control of asthma during pregnancy.
- The BTS guidelines make it clear that short-acting /long-acting beta 2-agonists, inhaled and oral corticosteroids should all be used as normal during pregnancy.
- The BNF advises that 'inhaled drugs, theophylline and prednisolone can be taken as normal during pregnancy and breast-feeding.

**Acute severe asthma Classification:**

Acute severe asthma are stratified into moderate, severe or life-threatening:

Moderate	Acute Severe	Life-threatening
<ul style="list-style-type: none"> <li>➤ <b>PEFR</b> &gt; 50% best or predicted.</li> <li>➤ <b>Speech</b> normal.</li> <li>➤ <b>RR</b> &lt; 25 / min</li> <li>➤ <b>HR</b> &lt; 110 bpm.</li> </ul>	<ul style="list-style-type: none"> <li>➤ PEFR 33 - 50% best or predicted.</li> <li>➤ <u>Can't complete sentences.</u></li> <li>➤ RR &gt; <b>25</b>/min.</li> <li>➤ Pulse &gt; <b>110</b> bpm.</li> </ul>	<ul style="list-style-type: none"> <li>➤ <b>PEFR &lt; 33%</b> best or predicted.</li> <li>➤ Oxygen sat &lt; 92%.</li> <li>➤ Silent chest, cyanosis or feeble respiratory effort.</li> <li>➤ Bradycardia, dysrhythmia or hypotension.</li> <li>➤ Exhaustion, confusion or coma.</li> </ul>

Indications of **life threatening asthma** by the guidelines, these are:

- 1) PEFR <33% best or predicted
- 2) SpO<sub>2</sub> <92%
- 3) PaO<sub>2</sub> <8 kPa
- 4) **Normal PaCO<sub>2</sub>** (4.5-6.0 kPa)
- 5) Silent chest
- 6) Cyanosis
- 7) Poor respiratory effort
- 8) Arrhythmia
- 9) Exhaustion, or
- 10) Altered conscious level.

Asthma + **normal or low PCO<sub>2</sub>** >>> **Life threatening asthma**, it is a warning of impending respiratory failure as the patient becomes too tired to ventilate adequately.

The BTS defines **near fatal asthma** as an attack with **raised PCO<sub>2</sub>** and/or **requiring mechanical ventilation** with raised inflation pressures.

A raised PaCO<sub>2</sub> is an important sign that **intubation** may be required if the patient is not responding to maximum medical management.

Non-invasive ventilation is **not** recommended in acute severe asthma.

**Acute severe asthma** >>> acute respiratory alkalosis with associated hypoxia (Hypoxia ↓PO<sub>2</sub>, ↓PCO<sub>2</sub>, alkalosis ↑PH).

Other D.D of **Hypoxia, Hypocapnea, Alkalosis**:

- 1) **Acute severe asthma.**
- 2) **Pulmonary embolism.**
- 3) **Anxiety hyperventilation syndrome** (but **NO** Hypoxia).

**British Thoracic Society (BTS) guidelines:**

- **Beta 2-agonists** should be administered as soon as possible, preferably **nebulised driven by oxygen**. Repeat doses should be given at 15-30 minute intervals, or **continuous nebulisation** can be used where there is inadequate response to bolus therapy.
- **Nebulised ipratropium bromide** should be added for patients with acute severe or life threatening asthma, or those with a poor initial response. Its addition produces significantly greater bronchodilation than a β<sub>2</sub>-agonist alone.
- **Oxygen** should be given to maintain saturations at **94-98%**. Patients with saturations **less than 92% on room air** should have an **ABG** to exclude hypercapnia. However, starting treatment should not be delayed to do the ABG. **Initially high-flow oxygen is used**, and then weaned to maintain adequate saturations. Unless you suspect COPD there isn't a need to be cautious with oxygen therapy.
- **Steroids** reduce mortality, relapses, subsequent hospital admission and requirement for β<sub>2</sub>-agonists. The earlier they are given in the attack, the better the outcome. A dose of **40-50mg** should therefore be given once oxygen and nebuliser therapy has been established. This should be continued **for 5 days, or until recovery**, and can then be **stopped abruptly unless** the patient has taken long-term oral corticosteroids.
- **Magnesium sulphate (MgSO<sub>4</sub>) IV** recommended as next step for patients who are not responding to SOS (Salbutamol inhalation + Oxygen + Steroids) (e.g. 2g IV over 20 mins). The mechanism by which it has its effect is not fully

understood, but it is thought that low magnesium levels in bronchial smooth muscle favour bronchoconstriction. The **RR should be over 25 breaths/min** in a patient with severe asthma who was not yet showing signs of respiratory fatigue.

- Little evidence to support use of **IV aminophylline** (although still mentioned in management plans).
- If no response consider IV salbutamol.
- **NB:** IV. MgSo4 is useful in acute severe asthma, rather than COPD.
- **NB:** RR **below** 25/min is **against** the need for MgSo4 IV in severe asthma.
- **NB:** Current guidelines do not support the routine use of non-invasive ventilation in asthmatics as they will need high pressures.
- **NB:** Non-invasive ventilation is **not** recommended in acute severe asthma.
- **NB:** A **pH less than 7.35** likely represents CO2 retention in a tiring patient and is an ominous sign in acute asthma >>> the strongest indicator of a need for intubation and ventilation.
- **NB:** Performing serial peak flows in a patient with life-threatening asthma is neither practical nor desirable.

### Occupational Asthma:

Episodic cough and wheeze with nocturnal symptoms are classical of asthma.

Occupational asthma is the commonest industrial lung disease with over 400 causes and accounts for **up to 10% of adult onset asthma**.

There are an estimated 1500 to 3000 cases of occupational asthma reported each year.

The commonest occupations affected are spray painters, bakers, chemical processors, plastics workers and welders and soldering.

Patients are **characteristically better when on holiday**.

Causes:

- **Isocyanates cobalt** - the most common cause. Example occupations include spray painting and foam moulding using adhesives.
- Platinum salts
- Soldering flux resin
- Epoxy resins
- Flour



- Formaldehyde, Glutaraldehyde, and Chlorhexidine.
- Proteolytic enzymes

Diagnosis:

**Serial** measurements of peak expiratory flow rate (**PEFR**) are recommended both at work and away from work.  
Recordings should be performed two hourly for 4 weeks or if this is not possible metacholine/histamine challenges can be undertaken after days at work and away from work.  
Bronchial provocation testing should only be undertaken in a specialized center.

TTT:

- 1) The most appropriate ttt firstly to **review of the work environment** to ensure that exposure to paint fumes are minimised.
- 2) If these changes do not improve his symptoms then he **should be offered alternative work (change the job)**.

### Nocturnal asthma

**EX:** female patient 25 years old has 10 months history of **nocturnal cough** and SOB, particularly first thing in the **morning**, chest wheezes, she has **GERD**, not smoker, Vitally stable, Normal CXR, **low PEFR**.

TTT:

- **Regular low dose inhaled steroids (Betamethasone)**.
- Previously was PPI and head elevation at bedtime.

### Exercise-induced asthma

It is best diagnosed with **spirometry before and after exercise**, where a typical obstructive pattern may be displayed following exercise.

No abnormalities may be displayed following bronchodilator therapy if it is true exercise-induced asthma. Similarly lung volumes and diffusion capacity are likely to be unaffected.

Blood gas analysis would be relatively unhelpful in this scenario as little change in partial pressures would be expected.

### **Pulmonary eosinophilia**

Causes of pulmonary eosinophilia:

- Churg-Strauss syndrome
- Allergic Broncho pulmonary aspergillosis (ABPA)
- Löffler's syndrome
- Eosinophilic pneumonia
- Hypereosinophilic syndrome
- Tropical pulmonary eosinophilia
- Drugs: nitrofurantoin, sulphonamides
- Less common: Wegener's granulomatosis

### **Churg-Strauss syndrome (CSS)**

Churg-Strauss syndrome is a **rare** vasculitis, it is an **ANCA** associated **small-medium** vessel vasculitis.

Incidence is approximately 2.5 cases per 100,000 adults per year.

The typical picture of a patient with CCS is asthma, allergic rhinitis, raised eosinophilic count and eosinophilic vasculitis, mild renal impairment, microscopic haematuria and raised IgE.

Asthma + Eosinophilia + Renal imp + Microscopic Haematuria + Nerve lesion >>> CSS
--

#### **Features:**

- 1) Asthma
- 2) Blood eosinophilia (e.g. > **10%**)
- 3) Paranasal sinusitis or abnormal growths (polyps).
- 4) Non- fixed Pulmonary infiltrates (may be transient)
- 5) Histological proof of vasculitis with **extravascular eosinophils by vascular biopsy**.
- 6) Mononeuritis multiplex occurs 75% of patients (e.g. ulnar nerve palsy with foot drop) or polyneuropathy.

- 7) pANCA positive in 60%, but their presence or absence is not diagnostic.
- 8) Serum IgE is very commonly elevated and correlates with disease severity.
- 9) Rarely, it can cause either an anterior or a posterior ischaemic optic neuropathy, which presents with visual loss.
- 10) Nephritic syndrome: hypertension, oedema and haematuria.

**ACR criteria** for the diagnosis of Churg-Strauss syndrome requires **4** of the following features:

- 1) Asthma
- 2) Eosinophilia greater than 10%
- 3) Paranasal sinus abnormality
- 4) Non-fixed pulmonary infiltrates visible on chest radiographs
- 5) Sensory mononeuropathy or polyneuropathy and
- 6) Blood vessels biopsy with extravascular eosinophils.

**Mortality/ Morbidity:**

- Mainly due to myocarditis and MI secondary to coronary arteritis.
- With ttt, the 1-year survival rate is 90% and the 5-year survival rate is 62%.
- Overall, without ttt, the 5-year survival rate is 25%.

**TTT:**

- **Glucocorticoids alone** usually are adequate.
- Immunosuppressant drugs (cyclophosphamide, azathioprine, MMF) are necessary in fewer than 20% of patients.
- Pulse steroid IV may be required in major life-threatening organ involvement.
- Others: IVIG, IFN-alpha and plasma exchange (debatable).

**NB:** Leukotriene receptor antagonists may precipitate the disease.

**Loffler's syndrome:**

- Transient CXR shadowing and blood eosinophilia.
- Thought to be due to parasites such as Ascaris lumbricoides causing an alveolar reaction.
- There is fever, cough and night sweats which often last less than 2 wks.
- Generally a self-limiting disease

**Tropical pulmonary eosinophilia:**

- Associated with *Wuchereria bancrofti* infection.

**Aspergillus**

Aspergillus is a fungus transmitted to humans via inhalation.

Hence, it primarily affects the lungs, causing **5** main syndromes:

- 1) **Asthma**: it is type **I** hypersensitivity reaction to fungal spores.
- 2) **ABPA (Allergic Broncho pulmonary Aspergillosis)**:
  - It is type **III** hypersensitivity reaction to *Aspergillus fumigatus*.
- 3) **Aspergilloma**:
  - It is a fungal ball within a pre-existing lung cavity that may have resulted from TB (an old tuberculous cavity), sarcoidosis, or other necrotizing pulmonary process.
  - It is usually asymptomatic but may cause cough, haemoptysis (in 75% of cases) and fever.
  - Precipitating antibodies help to confirm the diagnosis and are present in 95% of cases.
- 4) **Invasive aspergillosis (IA)**:
  - Aspergillosis is a fungal infection, and develops mainly in individuals who are immunocompromised.
  - It typically manifests with fever, cough, dyspnoea, and pleuritic chest pain in patients with prolonged neutropenia or immunosuppression, such as that which occurs after chemotherapy.
  - It is a leading cause of death in acute leukaemia and haemopoietic stem cell transplantation.
  - It is caused by haematogenous spread of the fungus.
  - CXR shows consolidation and the patient has rapidly progressing and worsening hypoxemia.
  - It is often seen on CXR and CT scan, and demonstrates an air crescent sign.
  - Definitive diagnosis is by microscopy and depends upon the demonstration of the organism in tissue.
  - H&E stain does not stain most of the fungi, except the *Aspergillus* species and the zygomycetes.
  - IA can only be confidently diagnosed by the finding of characteristic hyphae on a biopsy specimen.
  - Other investigations include the galactomannan test.
  - TTT:
    - Liposomal Amphotericin IV 3 mg/kg or
    - Voriconazole or
    - Caspofungin.

**EX:** Male pt. 25 years old post bone marrow transplantation due to CML, he has fever, lobar pneumonia on CXR, already on meronam and vancomycin, Labs: low TLC 0.2, Hb 9, PLT 12, negative blood and urine C&S >>> ? **Invasive Aspergillosis (IA)** for Amphotericin or Voriconazole or Caspofungin.

### **Semi-invasive aspergillosis:**

It is a chronic indolent disease that affects people with **mild immunosuppression** such as those with DM, COPD, alcoholics, and elderly or on prolonged steroid use.

If left untreated there is a significant associated mortality; however it is **difficult to diagnose due to its slow progression** both clinically and radiologically (i.e. may be with **normal CXR**).

Symptoms includes cough, wheezes, bronchitis and **haemoptysis in 15%**.

**EX:** Pt DM, alcoholic with 1 year history of cough, expectoration, haemoptysis

## **5) EAA (Extrinsic Allergic Alveolitis)**

### **Allergic Broncho pulmonary aspergillosis (ABPA)**

- It results from an allergy (hypersensitivity reaction) to Aspergillus spores.
- Immediate (type I) reactions occur in virtually all patients with ABPA following intradermal injections of Aspergillus fumigatus extracts, with only 16% developing delayed (type IV) reactions.
- It predominantly affects patients with cystic fibrosis, asthma, and bronchiectasis.
- It is a hypersensitivity reaction to Aspergillus in asthmatic people.
- It should always be exclude in people with asthma who have a raised eosinophil count.
- In the exam questions often give a history of bronchiectasis and eosinophilia.
- There is initially bronchospasm which can progress to proximal bronchiectasis and occasionally upper zone lung fibrosis like TB.
- Exacerbations are more common in the autumn and winter months.

Features:

- Bronchoconstriction: wheeze, cough, dyspnoea.
- Bronchiectasis (proximal).

Investigations:

- Eosinophilia
- Raised IgE
- Skin prick: Positive Radioallergosorbent (RAST) test to Aspergillus
- Positive IgG precipitins to Aspergillus in **70%** of patients. (not as positive as in aspergilloma)
- Fleeting CXR changes is due to intermittent obstruction of airways.

Management:

- 1) **Steroids oral**: is the mainstay of initial treatment
- 2) Itraconazole is sometimes introduced as a 2nd line ttt (additional prolonged courses of itraconazole up to 4 months may diminish the steroid requirement).

A 36-year-old man who is a known asthmatic complains of persistent cough and shortness of breath, which is unresponsive to his normal inhaled therapy. A CXR shows fibrosis of both upper lobes. HRCT: proximal bronchiectasis.

What is the most likely diagnosis? >>> **ABPA**

### **Aspergilloma**

An aspergilloma is a fungus ball which often colonises an existing lung cavity (e.g. secondary to TB, lung cancer or cystic fibrosis).

Usually asymptomatic but features may include:

- Cough
- **Haemoptysis** (may be severe)

Investigations:

- CXR containing a rounded opacity surrounded with a rim of air.
- **Serum high titres Aspergillus precipitins**

TTT:

- 1) **Surgical resection**: is the curative ttt
- 2) Long term Itraconazole: in patients not fit for surgery, it leads to resolution of the lesion in up to 60% of patients.
- 3) Arterial embolisation: where there is life threatening haemoptysis

### Eosinophilic pneumonia

It is a **rare** respiratory pathology characterized by **pulmonary infiltrates** plus **pulmonary eosinophilia**.

It can present acutely **AEP** (Acute Eosinophilic Pneumonia) over a few days or chronically **CEP** (Chronic Eosinophilic Pneumonia) over months to years.

It can be **idiopathic** or **secondary** to parasites, drugs or vasculitis.

**CEP** usually occurs in those aged in their **50s** with a **female** predominance.

About 60% of patients with CEP have asthma and 90% are non-smoker.

The peripheral eosinophilic count is **not** always raised.

The **serum IgG** is raised in two-thirds and the **ESR** is elevated.

**Sputum** and **BAL** often shown an **eosinophilia**.

#### CXR:

- AEP: bilateral diffuse infiltrates with effusion.
- CEP: bilateral dense **peripheral** infiltrates in the **OUTER** two-thirds of the lungs (i.e. often opposite to pulmonary oedema).

### Pulmonary function tests

Pulmonary function tests can be used to determine whether a respiratory disease is obstructive or restrictive.

Obstructive lung disease	Restrictive lung disease
FEV1 - significantly <u>reduced</u> FVC - <u>reduced</u> or normal FEV1% (FEV1/FVC) – <u>reduced</u> <b>FEV1/FVC &lt; 0.7</b>	FEV1 – <u>reduced</u> FVC - significantly <u>reduced</u> FEV1% (FEV1/FVC) - <u>normal</u> or <u>increased</u> <b>FEV1/FVC &gt; 0.7</b>
<ul style="list-style-type: none"> <li>➤ Asthma</li> <li>➤ COPD</li> <li>➤ Bronchiectasis</li> <li>➤ Bronchiolitis obliterans</li> </ul>	<ul style="list-style-type: none"> <li>➤ Pulmonary haemorrhage</li> <li>➤ Pulmonary fibrosis</li> <li>➤ Asbestosis</li> <li>➤ Sarcoidosis (↓ KCO)</li> <li>➤ Acute respiratory distress syndrome</li> </ul>

	<ul style="list-style-type: none"> <li>➤ Infant respiratory distress syndrome</li> <li>➤ Neuromuscular disorders</li> <li>➤ Kyphoscoliosis</li> <li>➤ Obesity</li> <li>➤ Pneumonectomy</li> </ul>
--	---

In restrictive lung disease due to respiratory muscle weakness the lung itself can function normally but muscle weakness will result in grossly **low** lung volumes including forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and total lung capacity (TLC).

However (RV) will be relatively high as a consequence of this weakness.

Consequently, RV/TLC will be elevated.

In **restrictive** lung disease >>> **Low VC, low TLC, high RV/TLC**

NB: In any patient with **FEV1 below 1** >>> there is high risk of **pneumothorax** if tried for **pleural tapping of effusion**, unless do under CT guidance. So **bronchoscopy** will be hopefully.

### Flow volume loop

A normal flow volume loop is often described as a 'triangle on top of a semi-circle' Flow volume loops are the most suitable way of assessing **compression** of the **upper** airway e.g. in **thyroid goiter or cancer**.

This may be present in up to 40% of patients with retrosternal goitre and generally requires at least 50% obstruction of the airway before symptoms arise.

Flow volume loop is the investigation of choice for **upper airway compression**.

### Transfer factor of the lung for carbon monoxide (TLCO)

- The transfer factor describes the rate at which a gas will **diffuse** from alveoli into blood.
- Carbon monoxide (CO) is used to test the rate of diffusion.
- Results may be given as the total gas transfer (**TLCO**) or that corrected for lung volume (transfer coefficient, **KCO**)
- **TLCO** = Lung CO transfer factor
- **KCO** = CO transfer coefficient (ml/m/mm Hg)



<u>Causes of a raised TLCO (4):</u>	<u>Causes of a lower TLCO</u>
<ul style="list-style-type: none"> <li>• <u>Asthma.</u></li> <li>• <u>Pulmonary haemorrhage: (Wegener's, Goodpasture's).</u></li> <li>• <u>Left-to-right cardiac shunts.</u></li> <li>• <u>Polycythaemia.</u></li> <li>• Male gender,</li> <li>• <b>Exercise.</b></li> <li>• Hyperkinetic states.</li> </ul>	<ul style="list-style-type: none"> <li>• Pulmonary fibrosis</li> <li>• Pneumonia</li> <li>• Pulmonary emboli</li> <li>• Pulmonary oedema</li> <li>• Emphysema</li> <li>• Anaemia</li> <li>• Low cardiac output</li> <li>• Sarcoidosis</li> </ul>

Transfer factor:

- **Raised**>>>> Asthma, Hge, Left-to-right shunts, Polycythaemia.
- **Low** >>>> everything else.

**NB:**

\* Where alveolar haemorrhage occurs the TLCO tends to increase due to the enhanced uptake of carbon monoxide by intra-alveolar haemoglobin.

\* KCO also tends to increase with age.

\* Some conditions cause an increased KCO with a normal or reduced TLCO:

- Pneumonectomy/lobectomy
- Scoliosis/kyphosis
- Neuromuscular weakness
- Ankylosis of costovertebral joints e.g. ankylosing spondylitis

Although the conventional single breath **diffusing** capacity (DLCO) has been accepted as a **standard non-invasive test** to assess the **integrity of pulmonary function**, there are numerous pitfalls in its use.

One such pitfall is the effect of carbon monoxide in **cigarette smoke**, which raises carboxy-haemoglobin (COHb) to as high as 10-15% (normal value 1-2%). Most regression values for DLCO are derived from the study of lifetime non-smokers, so that **the use of these in smokers underestimates** the percent of predicted DLCO values, unless additional adjustments are made.

**NB: Smoking >>> false decreasing** of DLCO values

So Smoking on the morning of the test, affects interpretation of the test.

**KCO** is the best test to confirm **restrictive** lung disease due to **parenchymal** disorder.

KCO will be **reduced** in **interstitial** lung disease.

Normal KCO would rule out significant restrictive lung disease as a cause with abnormal CT.

### Respiratory alkalosis: causes:

- Acute severe asthma
- Pulmonary embolism
- Anxiety leading to hyperventilation
- Salicylate poisoning\*
- CNS disorders: stroke, subarachnoid haemorrhage, encephalitis
- High altitude
- Pregnancy

**Salicylate** overdose leads to a **mixed respiratory alkalosis** and **metabolic acidosis**:

- **Early** stimulation of the respiratory centre leads to a respiratory alkalosis.
- Whilst **later** the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis.

### Respiratory acidosis: causes:

- COPD.
- Decompensation in other respiratory conditions e.g. Life-threatening asthma / pulmonary oedema.
- Sedative drugs: benzodiazepines, opiate overdose.

### COPD: causes

- Smoking.
- Alpha-1 antitrypsin deficiency.
- Other causes:
  - Cadmium (used in smelting)
  - Coal
  - Cotton
  - Cement
  - Grain

NB: Isocyanates are more associated with occupational asthma

### COPD: investigation and diagnosis

NICE recommend considering a diagnosis of COPD in patients over 35 years of age who are smokers or ex-smokers and have symptoms such as exertional breathlessness, chronic cough or regular sputum production.

The following investigations are recommended in patients with suspected COPD:

- Post-bronchodilator spirometry to demonstrate airflow obstruction: **FEV1/FVC ratio less than 70%**, with normal TLC (total lung capacity).
- Chest x-ray: hyperinflation, bullae, flat hemi-diaphragm. Also important to exclude lung cancer.
- CBC: exclude secondary polycythaemia.
- Body mass index (BMI) calculation.

The severity of COPD is categorised using the **FEV1\***:

Post-bronchodilator FEV1/FVC	FEV1 (%of predicted)	Severity
< 0.7	> 80%	Stage 1 - <b>Mild**</b>
< 0.7	<b>50-79%</b>	Stage 2 - <b>Moderate</b>
< 0.7	<b>30-49%</b>	Stage 3 - <b>Severe</b>
< 0.7	<b>&lt; 30%</b>	Stage 4 – <b>Very severe</b>

- FEV1 is used for assessment of severity of COPD, NOT FOR DIAGNOSIS.
- Measuring peak expiratory flow (PEFR) is of limited value in COPD, as it may underestimate the degree of airflow obstruction.
- Note that the grading system has changed following the 2010 NICE guidelines. If the FEV1 is greater than 80% predicted but the post-bronchodilator FEV1/FVC is < 0.7 >>> it is classified as Stage 1 (mild).
- Patients can now be diagnosed with 'mild' COPD if their FEV1 predicted is > 80% if they have symptoms suggestive of COPD.
- Symptoms should be present to diagnose COPD in these patients.
- The pathology is centrilobular or panacinar with **loss of elastic tissue recoil**.

### COPD: management of acute exacerbations

The most common bacterial organisms that cause infective exacerbations of COPD are:

- **Haemophilus influenzae** (most common cause)
- Streptococcus pneumoniae
- Moraxella catarrhalis

Respiratory viruses account for around 30% of exacerbations, with the human rhinovirus being the most important pathogen.

NICE guidelines from 2010 recommend the following:

- Increase frequency of bronchodilator use and consider giving via a nebuliser.
- Give prednisolone **30 mg daily** for 7-14 days. Prolonged courses offer no additional benefit.

- It is common practice for all patients with an exacerbation of COPD to receive antibiotics. NICE do not support this approach. They recommend giving oral antibiotics 'if sputum is purulent or there are clinical signs of pneumonia'.
- **NIV** should therefore be considered within the first 60 minutes of hospital arrival in all patients with an acute exacerbation of COPD in whom a respiratory acidosis persists despite maximal medical therapy (controlled O<sub>2</sub>, nebulised salbutamol and ipratropium, prednisolone, antibiotic (where indicated)).

- Pneumonia >>>>>> **Strep Pneumonia**
- Infective exacerbation of COPD >>>>>> **H. influenzae**

**EX:** Pt has COPD with palpitation with MAT >>> Stop Ventolin, low flow O<sub>2</sub>, Verapamil 5 mg IV then orally 40-120 mg/day TDS

### COPD: stable management

#### General management:

- Smoking cessation advice
- Annual influenza vaccination
- One-off pneumococcal vaccination every 5 years.

#### Bronchodilator therapy:

- Short-acting beta2-agonist (SABA) or short-acting muscarinic antagonist (SAMA) is first-line treatment.
- For patients who remain breathless or have exacerbations despite using short-acting bronchodilators the next step is determined by the FEV1.

#### FEV1 > 50% (Stage I & II):

- Long-acting beta2-agonist (LABA), for example salmeterol, **or:**
- Long-acting muscarinic antagonist (LAMA), for example tiotropium (Spiriva 18 Mcg ®) (there is increased risk of CVA has been identified).

**FEV1 < 50% (Stage III & IV):**

- LABA + high-dose inhaled corticosteroid (ICS) in a combination inhaler, or:
- LAMA.

**COPD - still breathless** despite using salbutamol inhalers as required:

**If FEV1 > 50 %:**>>> LABA or LAMA

**If FEV1 < 50 %:**>>> (LABA + ICS) or LAMA

**For patients with persistent exacerbations or breathlessness:**

- If taking a LABA then switch to a LABA + ICS combination inhaler
- Otherwise give a LAMA and a LABA + ICS combination inhaler
- Also, pulmonary rehabilitation therapy.

COPD >> using of **high-dose ICS** >>>> to reduced exacerbations frequency, improve quality of life and reduce hospitalisation rates, at the expense of increased pneumonia.

ICS usage in COPD does **not** improve long term **prognosis**, as they do not slow the rate of decline of FEV<sub>1</sub>.

**Oral theophylline:**

- NICE only recommends theophylline after trials of short and long-acting bronchodilators or to people who cannot use inhaled therapy.
- The dose should be reduced if macrolide or fluoroquinolone antibiotics (enzyme inhibitors) are co-prescribed.

**Mucolytic:**

- Should be 'considered' in patients with a chronic productive cough and continued if symptoms improve.

Factors which may improve survival in patients with stable COPD:

- 1) Smoking cessation - the single most important intervention in patients who are still smoking.

- 2) (LTOT) Long term oxygen therapy in patients who fit criteria.
- 3) Lung volume reduction surgery in selected patients:
  - If **PCO<sub>2</sub> ≥ 7.4**
  - Severe limitation of exercise capacity despite maximal therapy.
  - Predominant upper lobe emphysema.
  - Persistent symptoms despite a period of pulmonary rehabilitation.

The upper cut off for referral for COPD lung volume reduction surgery for **pCO<sub>2</sub> is 7.3**; as such he is unsuitable for referral.

**Cor pulmonale:**

- Features include peripheral oedema, ↑JVP, systolic parasternal heave, loud P2.
- Use a **loop diuretic** for oedema.
- Consider long-term oxygen therapy (**LTOT**).
- ACEIs, CCBs and alpha blockers are not recommended by NICE.

**COPD: Long-Term Oxygen Therapy (LTOT)**

The 2010 NICE guidelines on COPD clearly define which patients should be assessed for and offered long-term oxygen therapy (LTOT). Patients who receive LTOT should breathe supplementary oxygen for **at least 15 hours a day**. Oxygen concentrators are used to provide a fixed supply for LTOT.

Assess patients if any of the following:

- Very severe airflow obstruction (FEV1 < 30% predicted). Assessment should be 'considered' for patients with severe airflow obstruction (FEV1 30-49% predicted).
- Cyanosis
- Polycythaemia
- Peripheral oedema
- Raised jugular venous pressure
- Oxygen saturations less than or equal to 92% on room air

Assessment is done by measuring arterial blood gases on 2 occasions at least 3 weeks apart in patients with stable COPD on optimal management.

**LTOT should be offered to COPD patients with:**

**A PO<sub>2</sub> of < 7.3 kPa (55 mmHg)**

**OR those with PO<sub>2</sub> of 7.3 - 8 kPa (60 mmHg) and ONE of the following:**

- Secondary polycythaemia
- Pulmonary hypertension
- Nocturnal hypoxemia
- Peripheral oedema (Cor-pulmonale)

COPD >> LTOT>>>>>>> if **2** measurements of **PO<sub>2</sub> < 7.3 kPa at least 3 weeks apart**, and

**ABG** should be performed in a **stable state and free from exacerbation**, which should be at **least 4 weeks after** an exacerbation of the disease.

Adequate data for **LTOT** prolonging **survival** exist **only for** COPD although in practice it is assumed to apply in other chronic hypoxemic lung conditions.

NICE guidance does **not** allow home O<sub>2</sub> therapy (LTOT) based on PH, PCO<sub>2</sub>, FEV<sub>1</sub> or exacerbation criteria.

**Benefits of LTOT:**

- ↓ Secondary polycythaemia.
- ↓ Sympathetic outflow.
- ↓ Salt and water retention.
- ↓ Cardiac arrhythmia.
- Improve sleep quality due to reduced hypoxia-induced sleep arousals.



### **Oxygen therapy**

**In patients who are critically ill (anaphylaxis, shock etc.) oxygen should initially be given via a reservoir mask at 15 l/min. Hypoxia kills.**

The BTS guidelines specifically exclude certain conditions where the patient is acutely unwell (e.g. myocardial infarction) but stable.

#### **Oxygen saturation targets:**

- Acutely ill patients: **94-98%**.
- Patients at risk of hypercapnia (e.g. COPD patients): **88-92%**.
- Oxygen should be reduced in stable patients with satisfactory oxygen saturation.

Any Pt with **COPD >>> Contraindicated High** flow Oxygen.

Patient with acute exacerbation of COPD and suffering from hypoxia and hypercapnia >>> the **respiratory centre** was **solely stimulated by hypoxia**. That is why his respiratory effort will become less and the condition worsened when he was given **high concentration oxygen, depriving him of hypoxic drive**.

#### **Management of COPD patients:**

- Prior to availability of blood gases, use a **28% Venturi mask at 4 l/min** and aim for an oxygen saturation of **88-92%** for patients with risk factors for hypercapnia but no prior history of respiratory acidosis.
- Adjust target range to **94-98%** if the pCO<sub>2</sub> is normal.

NB: Target O<sub>2</sub> Sat% in COPD:

- **88-92%** IF associated with HIGH PCO<sub>2</sub>
- **94-98%** IF associated with NORMAL PCO<sub>2</sub>

NB: When managing patients with COPD, once the pCO<sub>2</sub> is known to be normal the target oxygen saturations should be 94-98%.

**Situations where oxygen therapy should NOT be used routinely if there is no evidence of hypoxia:**

- Acute coronary syndromes (MI)
- Stroke
- Obstetric emergencies
- Anxiety-related hyperventilation

**Non-invasive ventilation (NIV)**

NIV is the treatment of choice for **persistent hypercapnic** ventilation failure despite optimal medical therapy.

It has been shown in RCTs to reduce intubation rate and mortality in COPD patients with decompensated respiratory acidosis (pH <7.35 and pCO<sub>2</sub> >6 kPa).

NIV should therefore be considered **within the first 60 minutes** of hospital arrival in all patients with **an acute exacerbation of COPD** in whom a **respiratory acidosis persists** despite maximal medical therapy (controlled oxygen, nebulised salbutamol and ipratropium, prednisolone, antibiotic where indicated).

**Key indications:**

- 1) COPD with respiratory acidosis pH 7.25-7.35.
- 2) Type II respiratory failure secondary to chest wall deformity, neuromuscular disease or obstructive sleep apnoea
- 3) Cardiogenic pulmonary oedema unresponsive to CPAP
- 4) Weaning from tracheal intubation

**Recommended initial settings for bi-level pressure support (bi-PAP) in COPD:**

- Expiratory Positive Airway Pressure (**EPAP**): 4-5 cm H<sub>2</sub>O
- Inspiratory Positive Airway Pressure (**IPAP**): RCP advocate 10 cmH<sub>2</sub>O whilst BTS suggest 12-15 cm H<sub>2</sub>O. IPAP should be increased by 2-5 cm increments every 10 minutes, with a usual target of 20 cmH<sub>2</sub>O or until a therapeutic response is achieved.
- Back up rate: 15 breaths/min
- Back up inspiration: expiration ratio: (I:E ratio 1:3)
- FiO<sub>2</sub> not > 40%.
- Keep SpO<sub>2</sub> 88 - 92%

- ABG every 1-2 hr. ABGs should be repeated after 1 hour of NIV therapy, and 1 hour after subsequent change in settings or 4 hours in stable patients.

If the **pH is < 7.25** >>>> **invasive** ventilation should be considered.

A trial of NIV may be undertaken in bronchiectasis but should not be used routinely as its effectiveness is likely to be limited by excessive secretions

### **Exceptions for NIV may be:**

- **Haemodynamic instability** that is requiring **inotropes**.
- **Life threatening hypoxaemia** (when invasive ventilation may be more appropriate).
- Confusion / **impaired consciousness**
- Severe cognitive impairment (where NIV is not tolerated)
- Severe co-morbidity
- Facial burns/trauma/surgery
- Vomiting
- Fixed upper airway obstruction
- Undrained pneumothorax
- Upper GI surgery
- Unprotected airway,
- **Copious respiratory secretions**

### **Hospital at home (HaH) treatment for COPD**

A specific subtype of intermediate care is Hospital at Home (HaH), where active treatment is provided by healthcare professionals in the patient's home for a condition that otherwise would require hospital care.

BTS has issued recommendations as to whom HaH should be offered.

It recommends that HaH should **not** be offered in the below instances:

- 1) Impaired level of consciousness.
- 2) Acute confusion.

- 3) PH <7.35, if ABG have been measured.
- 4) Acute changes on chest radiograph.
- 5) Concomitant medical problem requiring inpatient stay.
- 6) Insufficient social support, no telephone, residence geographically removed from hospital.
- 7) New hypoxaemia (SpO<sub>2</sub> 90%) - a contraindication if oxygen cannot be provided at home.

Although factors such as increasing age and duration of COPD have been shown in studies to identify those at increased risk of relapse, they have only a moderate sensitivity and specificity, and hence are not included in the listed contraindications.

Patient with **COPD** and want to travel by airport to japan. What would you advise him to **check his fitness to fly**?

A **hypoxic challenge test** gives the patient **FiO<sub>2</sub> 15%** for **15 minutes** and measures **PO<sub>2</sub>**:

- If **PaO<sub>2</sub> > 7.4 kPa (> 55 mmHg)** - **Oxygen not required.**
- If **PaO<sub>2</sub> 6.6-7.4 kPa (50-55 mmHg)** - Borderline. A walk test may be helpful.
- If **PaO<sub>2</sub> < 6.6 kPa (< 50 mmHg)** - In-flight oxygen (2L/min).

Also simply History, examination, assessment of severity of COPD and **O<sub>2</sub> sat at sea level** should be performed:

- Sea level **SpO<sub>2</sub> > 95%** - **Oxygen not required**
- Sea level SpO<sub>2</sub> 92-95% and no risk factor - Oxygen not required
- Sea level SpO<sub>2</sub> 92-95% and additional risk factor - Perform hypoxic challenge test with arterial or capillary measurements
- Sea level SpO<sub>2</sub> < 92% - In-flight oxygen
- Receiving supplemental oxygen at sea level - Increase the flow while at cruising altitude.

**NB:** COPD with infective exacerbation: usually develop **respiratory acidosis**, so check **HCO<sub>3</sub>** if still normal so this is **acute** respiratory acidosis and may need **(Bi-PAP) NIPPV** (non-invasive positive pressure ventilator), alternative include

**Doxapram IVI**, a central respiratory stimulant, these would be combined with appropriate antimicrobial therapy. It should only be used **when Bi-PAP is unavailable** or in the case of **reduced respiratory drive due to** sedative or anaesthetic agents. Doxapram also has a number of contraindications, which include **HTN** (relative contraindications).

**EX: Spirometry and reversibility** is the investigation of choice in patients with asthma, smoker and farmer:

An **obstructive** defect **with** reversibility >>> **Asthma**

An **obstructive** defect **without** reversibility >>> **COPD**

A **restrictive** defect >>> would support a diagnosis of **farmer's lung**

### **Obstructive sleep apnoea/hypopnoea syndrome (OSAHS)**

It affects 1-2 % of the population and is most commonly found in **obese male smokers** with a background of **COPD**

#### **Predisposing factors:**

- Obesity
- Macroglossia: **acromegaly**, **hypothyroidism**, amyloidosis
- Large tonsils and nasal deformities.
- Marfan's syndrome

Sleep apnoea causes include >> obesity and macroglossia

#### **Consequence:**

- **Daytime somnolence**: The dominant symptom
- **Apnoea** many times per **night**, resulting in **reduction of REM sleep**
- **Hypertension**
- Impaired glucose tolerance (IGT), and **insulin resistance**.
- True nocturnal polyuria.
- **Cushing's syndrome**.
- It is an independent risk factor for **stroke** and **death**.

**Assessment of sleepiness:**

- Epworth Sleepiness Scale (ESS) - questionnaire completed by patient +/- partner.
- Multiple Sleep Latency Test (MSLT) - measures the time to fall asleep in a dark room (using EEG criteria).

**Diagnostic tests:**

- The diagnosis can usually be made by a **good history** from the sleeping partner, supported by **non-invasive oximetry** performed at home (**overnight home sleep oximetry**).
- Polygraphic sleep studies (full polysomnographic studies): ranging from monitoring of pulse oximetry at night to full polysomnography where a wide variety of physiological factors are measured including EEG, respiratory airflow, thoraco-abdominal movement, snoring and pulse oximetry. This full polysomnographic studies are rarely required for diagnosis but can be useful for research purposes.

**Management:**

- Weight loss.
- CPAP is first line for moderate or severe OSAHS: dramatic effect.
- Intra-oral devices (e.g. mandibular advancement) may be used if CPAP is not tolerated or for patients with mild OSAHS where there is no daytime sleepiness.
- Limited evidence to support use of pharmacological agents.

**Alpha-1 antitrypsin deficiency (A1AT)**

Alpha-1 antitrypsin (A1AT) deficiency is a common inherited condition caused by a **lack of a protease inhibitor (Pi)** normally produced by the **liver**.

The role of A1AT is to protect cells from enzymes such as neutrophil elastase.

Genetics:

- Located on chromosome **14**
- Inherited in an **autosomal recessive / autosomal co-dominant fashion** (trusted sources are split on which is a more accurate description).
- Alleles classified by their electrophoretic mobility:

(**M** for normal, **S** for slow, and **Z** for very slow)

- Normal = PiMM
- Homozygous PiSS (**60%** normal A1AT levels)
- Homozygous PiZZ (**10%** normal A1AT levels)

The genotype **PiZZ** is associated with the **most severe form** of alpha 1-antitrypsin deficiency as the circulating levels of A1AT are 10-15% of normal.

Cigarette smoking is especially harmful to those with A1AT deficiency and can accelerate the progression of emphysema by 10 years.

The serum levels of some of the common genotypes are:

- **PiMM: 100%** (normal)
- PiMS: 80% of normal serum level of A1AT
- **PiSS: 60%** of normal serum level of A1AT
- PiMZ: 60% of normal serum level of A1AT
- PiSZ: 40% of normal serum level of A1AT
- **PiZZ: 10-15%** (severe alpha 1-antitrypsin deficiency).

NB: Heterozygote patients such as those with the PiMZ genotype have alpha-1 antitrypsin levels approximately 35% of normal. They therefore have a low risk of developing clinically evident lung disease.

A1AT deficiency is an autosomal co-dominant disorder - both alleles contribute to the phenotype. The most common allele is **M (normal)**, whilst there are **over 100 abnormal alleles** (leading to decreased A1AT levels) the most common are Z and S.

Individuals with a single normal allele may have reduced levels of A1AT but still produce sufficient normal protein to prevent development of a disease phenotype, this is why some texts will refer to the condition as **autosomal recessive**.

**Features:**

- Patients who manifest disease usually have **PiZZ** genotype
- Lungs: panacinar emphysema, most marked in lower lobes
- **Liver: cirrhosis** and **hepatocellular carcinoma** in adults, cholestasis in children.
- A1AT deficiency is associated with a number of **malignancies** including **hepatocellular** cancer, **lung** cancer, **bladder** cancer and **lymphoma**.
- Other associated conditions include
  - Pancreatitis
  - Gall stones
  - **Primary sclerosing cholangitis (PSC)**
  - COPD
  - Bronchiectasis
  - Wegener's granulomatosis and
  - Pelvic prolapse.

<b>Young pt. with COPD + non-smoker + family history + Liver &gt;&gt;&gt; A1AT.</b>
---

**Investigations:**

- **A1AT concentrations**

**Management:**

- No smoking
- Supportive: bronchodilators, physiotherapy
- IV recombinant alpha1-antitrypsin protein concentrates
- Surgery: volume reduction surgery, lung transplantation



### Pneumonia: prognostic factors

#### CURB-65 criteria of severe pneumonia:

- **Confusion** ( AMT = Abbreviated Mental Test score  $\leq 8/10$ )
  - **Urea**  $> 7$  mmol/L
  - **Respiratory rate**  $\geq 30$  / min
  - **BP**: systolic  $\leq 90$  or diastolic  $\leq 60$  mmHg
  - **Age**  $\geq 65$  years
- Score of **0 or 1** are at low risk of death, and can be treated at **home** if the social circumstances are compatible.
- A score of **2** usually indicates **inpatient** treatment is required, but hospital-supervised outpatient treatment can be considered.
- Patients who have a CURB-65 score of **3 or more** are at high risk of death and have a severe pneumonia
- Those with scores of **4 and 5** should be for treatment in **ICU**.

(CURB-65) and its associated mortality rates:

- **Low** severity: CURB-65 **0-1**, mortality **<3%** >>> **Home ttt**
- **Moderate** severity: CURB-65 **2**, mortality **9%** >>> **Inpatient**
- **High** severity: CURB-65 **3-5**, mortality **15-40%** >>> **ICU**

A score of 0-1 is associated with a risk of mortality of **< 5%** from CAP.

A score of 2, the risk of mortality rise to be **13%**.

A score of 3, the risk of mortality rise to be **17%**.

A score of 4, the risk of mortality rise to be **42%**.

A score of 5, the risk of mortality rise to be **57%**

Other less important factors associated with a poor prognosis include:

- Coexisting disease (Comorbidity): DM, IHD, CHF, CVS, Renal imp.
- Hypoxemia (SPO<sub>2</sub>  $< 92\%$ , PO<sub>2</sub>  $< 8$  kPa) regardless of FiO<sub>2</sub>.
- Cyanosis.
- TLC:  $< 4000$  or  $> 20,000$  (**NOT Platelets** count).
- Temperature less than  $35^{\circ}\text{C}$  or more than  $40^{\circ}\text{C}$ .

- CXR: Multi-lobar infiltration
- Positive blood culture

### **Community-acquired Pneumonia (CAP)**

Community acquired pneumonia (CAP) may be caused by the following infectious agents:

- **Streptococcus pneumoniae** (accounts for around **80%** of cases)
- Staphylococcus aureus: commonly after the 'flu, ttt: Flucloxacillin or IV vancomycin.
- Haemophilus influenzae: is rare in patient age > 6 years, unless immunocompromised.
- Atypical pneumonias (e.g. due to Mycoplasma, legionella).
- Viruses.

***Streptococcus pneumoniae* (pneumococcus)** is the most common cause of community-acquired pneumonia

Characteristic features of pneumococcal pneumonia

- Rapid onset
- High fever
- Pleuritic chest pain
- Herpes labialis

<i>Streptococcus pneumoniae</i> >>> reactivation of the HSV >>> 'cold sores'
--

### **Management:**

The British Thoracic Society published guidelines in 2009:

<b>CURB 0-1</b> (low severity) can be treated with <b>amoxicillin</b> 500 mg TDS PO.
--

<b>CURB 2</b> should be treated with <b>amoxicillin</b> 500 mg to 1 g TDS + <b>clarithromycin</b> 500 mg BID.
---

<b>CURB 3-5</b> (High severity) should be treated as soon as possible with: <b>co-amoxiclav</b> 1.2 g IV TDS + <b>clarithromycin</b> 500 mg IV BD.
--

In the majority of patients CAP should be confirmed by **chest radiography before** the commencement of antibiotics.

However, if patients are **critically unwell** they should be treated for the presumptive diagnosis. Antibiotic treatment should be **initiated within 4 hours of presentation**.

The **oral** route is recommended in those with low and moderate severity CAP.

Patients treated with **parenteral** antibiotics initially should be **switched** to an **oral** regimen **once clinical improvement** is seen and the patients has been **afebrile for at least 24 hours**.

For most patients with **uncomplicated** CAP **7 days** of antibiotic treatment is recommended.

For those with **high severity pneumonia** where an organism has not been identified, **7-10 days** treatment is indicated and extended to **14-21 days** where clinically needed.

- **Low or moderate severity CAP:** oral amoxicillin+ macrolide should be added for patients admitted to hospital
- **High severity CAP (CURB  $\geq$  3/5):**
  - IV co-amoxiclav + IV clarithromycin
  - OR cefuroxime + clarithromycin
  - OR cefotaxime + clarithromycin

<b>Staph aureus</b> >> ttt: <b>co-prescription</b> <u>Amoxicillin + Flucloxacillin</u> ( <b>FLUMOX</b> )
--

Pneumonia in an <b>alcoholic</b> – <b>Klebsiella</b>
--

- |   |
|---|
| <ul style="list-style-type: none"><li>➤ <b>Klebsiella</b> pneumonia (<b>Friedlander's pneumonia</b>) typically occurs in middle-aged <b>alcoholic</b> men.</li><li>➤ CXR features may include <b>abscess</b> formation in the <b>upper/middle</b> lobes and empyema.</li><li>➤ The mortality rates are high approaches 30-<b>50%</b> regardless of treatment.</li></ul> |
|---|

It is important for patients who had **pneumonia** and had a **consolidation** on chest x ray to have a **follow up chest x ray in 6 weeks** to ensure complete resolution. This is to exclude any underlying cause especially malignancy.

Note that: The most useful test to support your suspicious of diagnosis of empyema is >>> **Pleural PH less than 7.2**, it is **highly suggestive of empyema**.

NB: Pleural fluid microbiology and C&S are often not useful as organisms frequently do not grow.

NB: Pleural WBCs can be raised even in reactive pleural effusion.

NB: Pneumococcal antigen either in serum or urine could be negative and would not confirm whether the effusion is infected or reactive.

### Hospital-acquired pneumonia (HAP)

- **Within 5 days of admission**: co-amoxiclav or cefuroxime.
- **More than 5 days after admission**:
  - Piperacillin with tazobactam (e.g. tazocin).
  - OR a broad-spectrum cephalosporin (e.g. ceftazidime).
  - OR a quinolone (e.g. ciprofloxacin).

### Legionella Disease (LD)

- **Legionnaire's disease** is caused by the intracellular bacterium Legionella pneumophila (Gm -ve bacilli).
- It occurs in 2-15% of community acquired pneumonia.
- It has an incubation period of 2-10 days.
- It is typically colonizes water tanks and hence questions may hint at air-conditioning systems, showers or **foreign holiday e.g. to Spanish**.
- Person-to-person transmission is not seen.
- Legionella is not sensitive to penicillin.
- Legionella resistance to rifampicin.

Features:

- Flu-like symptoms
- **Dry** cough
- Confusion
- Relative bradycardia

- TLC may be high or low
- Lymphopaenia, with marked leucocytosis.
- Hyponatraemia (dt SIADH) >>>ttt: Normal saline
- **Deranged liver function tests** and low ALP
- 50% of cases have **GIT** symptoms: ANV, Diarrhea, Abd pain.
- CXR: Bilateral patchy consolidation ± pleural effusion (in up to 50%).
- Urine: proteinuria, haematuria and myoglobinuria.

Diagnosis: **Urinary antigen test for legionella.**

It is the most useful test being rapidly available and accurate (70% specificity and 100% sensitivity).

The mortality rate may approach 100% in patients with underlying disease. In untreated patients, the mortality rate may be as high as 80%.

Management:

- **Macrolides** are appropriate first line therapy e.g. **Clarithromycin** or Erythromycin.
- **Fluoroquinolones** and **doxycycline** are reasonable alternatives.
- TTT of hyponatremia with legionnaire's >>> **Normal saline.**

It should be suspected in case of foreign travel or stay in hotels, failure to respond to penicillins, diarrhoea accompanying respiratory symptoms, deranged liver function tests and low sodium.

### **Mycoplasma pneumoniae**

- Mycoplasma pneumoniae is a cause of atypical pneumonia which often affects younger patients frequently among those living in boarding houses (housings, hostels).
- Epidemic pneumonia due to Mycoplasma infection is seen occasionally, example as class mates have recently been ill.
- Epidemics of Mycoplasma pneumoniae classically occur every 4 years.
- It is associated with a number of **characteristic complications** such as erythema multiforme (target lesion) and cold autoimmune haemolytic anaemia due to presence of anti-I antibody.
- It is important to recognise atypical pneumonias as they may not respond to penicillins or cephalosporins due to it lacking a peptidoglycan cell wall (NO cell wall).

**Features:**

- The disease typically has a prolonged and slow onset of symptoms
- Flu-like symptoms classically PRECEDE a dry cough
- Bilateral consolidation on CXR
- The CXR findings are much worse than the clinical findings.
- Complications may occur as below

**Complications (Extra-pulmonary manifestations): in up to 10% of cases:**

- **Haema:** Cold agglutinins (IgM antibodies) (In **50%** of cases) (which is directed against the I antigen of the erythrocyte membrane) and may cause a haemolytic anaemia (↓Hb, fragmented RBCs, ↑RTX, ↑ bilirubin), thrombocytopenia.
- **Skin:** Erythema multiforme, erythema nodosum.
- Bullous myringitis: painful vesicles on the tympanic membrane with erythematous ear ± occipital lymphadenopathy.
- **Neuro:** Meningoencephalitis, Guillain-Barre syndrome, Transverse myelitis, Cerebellar ataxia.
- **Heart:** Pericarditis/myocarditis
- **GIT:** hepatitis, pancreatitis
- **Renal:** acute glomerulonephritis (haematuria)

**Investigations:**

- Diagnosis is generally by **Mycoplasma serology**
- Positive cold agglutination test
- Positive coombs in 50 – 70% after 10 days of infection (it should be used with caution or not at all since 50% of the tests are false positive)
- Lack of bacteria in a gram-stained sputum.
- Lack of growth on blood agar.
- PCR.

**Management:**

- Clarithromycin/ Erythromycin.

- Tetracyclines such as **doxycycline** are an alternative if allergic/intolerant to macrolides/ fear of LQTS.

NB: Pneumococcus may also cause erythema multiforme.

The flu-like symptoms, slow progression of symptoms, bilateral consolidation, haemolytic anaemia and erythema multiforme point to a diagnosis of Mycoplasma. The most appropriate diagnostic test is Mycoplasma serology.

### **HIV: Pneumocystis jiroveci pneumonia**

Whilst the organism Pneumocystis carinii is now referred to as Pneumocystis jiroveci, the term Pneumocystis carinii pneumonia (PCP) is still in common use

- Pneumocystis jiroveci is a **unicellular eukaryote**, generally classified as a fungus but some authorities consider it a protozoa.
- Although PCP is officially a **fungal** infection it does not respond to anti-fungal medications.
- The organism is confined to the **alveolar space** of the lung and produces **debris** and **cysts** in the alveolar space with **interstitial** infiltration of lymphocytes and plasma cells so it can cause profound disturbance of O<sub>2</sub> exchange and **fatal hypoxaemia** if left untreated.
- PCP >>> **Interstitial pneumonitis** with **foamy intra-alveolar** exudate.
- PCP is the most common opportunistic infection in AIDS and those post-organ transplant (like post renal TX Pneumonia).
- All patients with a CD4 count < 200/mm<sup>3</sup> should receive PCP prophylaxis.
- **Co-trimoxazole (TMP-SMX)** (Trimethoprim-Sulfamethoxazole) is the **first line prophylactic** agent.
- Prophylaxis should be used in immunosuppressed patients who are at risk of developing PCP: all those with a CD4 count of <200, patients started on high dose steroids, those on chemotherapeutic regimens associated with significant immunosuppression and post renal TX..

Clinically it presents with **several weeks' history** of Dyspnoea, Dry cough, Fever, Very few chest signs (Normal chest auscultation), **typically, patients desaturate markedly on exertion.**

Pneumothorax is a common complication of PCP.

P.jiroveci can disseminate via the lymphatic and haematogenous routes to affect the thyroid, liver, bone marrow, lymph nodes and spleen.

Extra pulmonary manifestations are rare (1-2% of cases), may cause:

- Hepatosplenomegaly
- Lymphadenopathy
- Choroid lesions

Investigation:

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal CXR.
- So a normal chest x-ray does not exclude the diagnosis.
- Exercise-induced desaturation.
- Sputum often fails to show PCP, bronchoalveolar lavage (**BAL**) often needed to demonstrate PCP (**silver** stain shows characteristic **cysts**).

**Definitive diagnosis** of PCP in HIV is by bronchial alveolar lavage (**BAL**) ± **Trans-bronchial biopsy** with **silver** staining which shows characteristic **cysts**.

NB: Open lung biopsy is gold standard, but rarely performed in clinical practice.

Management:

- 1) **Co-trimoxazole** oral or IV for 21 days in HIV +ve cases and less duration in other causes of immunosuppression.
- 2) **IV pentamidine** in severe cases and if intolerant to co-trimoxazole.
- 3) If resistant to TMP-SMX, the **combination of clindamycin and primaquine** is likely to be more effective than IV pentamidine.
- 4) **Steroids if hypoxic** (if  $pO_2 < 9.3kPa$  as steroids reduce risk of **respiratory failure** by 50% and death by a third).

**EX: Pregnant female with HIV + PCP >>> ttt TMP-SMX**

TMP-SMX is the preferred initial therapy during pregnancy according to consensus guidelines.

The BNF states that there is a teratogenic risk in the 1st trimester (as trimethoprim is a folate antagonist), and neonatal haemolysis and methaemoglobinaemia in the 3rd trimester.

However, there is also considerable risk of harm to the foetus if the mother is unwell. The benefits in this situation therefore outweigh the risks, and it should be used.



**ARDS (Acute Respiratory Distress Syndrome)**

It is a **severe** form of Acute Lung Injury (**ALI**) which describes a pulmonary syndrome characterised by **non-cardiogenic pulmonary oedema**.

It is caused by increased **permeability** of alveolar capillaries leading to fluid accumulation in alveoli (i.e. non-cardiogenic pulmonary oedema) >>> exudation of **high protein rich fluid** into the interstitium and alveoli.

ARDS >>> **High protein pulmonary oedema**

In addition there is a **deficiency in surfactant** which **reduces** lung **compliance** and predisposes to **collapse** (especially in dependent zones).

It tends to be a **type 1** respiratory failure, rather than type 2.

**CXR** >>> classically shows **bilateral peripheral** interstitial and alveolar infiltrates that become progressively more confluent but **spare** the costophrenic angles.

The following are helpful in differentiating ARDS from other conditions, such as LVF:

- Normal heart size.
- Absent septal lines.
- Air bronchograms, and
- Peripheral distribution.

**Criteria (American-European Consensus Conference):**

- 1) Acute onset
- 2) **Bilateral** infiltrates on CXR
- 3) PO<sub>2</sub>/FiO<sub>2</sub> < 200 mmHg
- 4) Non-cardiogenic (pulmonary artery wedge pressure needed if doubt)
- 5) **Low PCWP** Pulmonary capillary wedge pressure (**less** than 18 mmHg).

**Causes**

- Infection: sepsis, pneumonia
- Massive blood transfusion
- Trauma
- Smoke inhalation injury
- **Pancreatitis**
- Cardio-pulmonary bypass

**Direct pulmonary causes of ARDS include:**

- Inhalation of gastric contents (pH <2)
- Infective (pneumonia, **TB**)
- Pulmonary trauma
- **Near drowning**
- Toxic gas inhalation and
- Oxygen toxicity.

**Indirect causes include:**

- Sepsis
- Non-thoracic trauma
- Uraemia
- Bowel infraction
- **Anaphylaxis** and
- **Burns.**
- **Post arrest**

ARDS <b>mortality</b> is generally <b>high (40%)</b> , but is determined by the cause with aspiration pneumonia having a mortality rate of almost 80% when associated with ARDS.
--

Management is by **mechanical ventilation** with **maximal** ventilatory therapy (Her inspired oxygen (**FiO<sub>2</sub>**) is **100%**, positive end expiratory pressure (**PEEP**) is **15 cmH<sub>2</sub>O** and **peak pressure** is **40 cmH<sub>2</sub>O**).

The mild high CO<sub>2</sub> is a reflection of **permissive hypercapnia** to prevent over distension of the lungs with high tidal volumes.

IF but is still hypoxic (low SPO<sub>2</sub>) Treatment of these patients used to be extremely difficult, with no significant improvement in prognosis seen with any technique. However, in 2010 the CESAR trial demonstrated a significant increase in survival without significant disability with the use of **extracorporeal membrane oxygenation (ECMO)**.

ECMO involves connecting a patient's circulation to an **external oxygenator** and **pump**, via a **catheter** placed in the **right** side of the heart. It requires the continuous

**infusion of anticoagulant**, and as such **bleeding** is the most commonly associated complication. Infection and haemolysis are also a risk.

**Prone positioning** is **controversial** and not yet widely accepted in clinical practice, although this may change in the future.

### **Bronchiectasis**

Bronchiectasis describes a permanent dilatation of the airways secondary to chronic infection or inflammation. There are a wide variety of causes are listed below:

#### **Causes:**

- Post-infective: tuberculosis, measles, pertussis, pneumonia.
- Cystic fibrosis.
- Bronchial obstruction e.g. lung cancer/foreign body.
- Immune deficiency: selective IgA, hypogammaglobulinaemia.
- Allergic Broncho pulmonary aspergillosis (ABPA).
- Ciliary dyskinetic syndromes: Kartagener's syndrome, Young's syndrome.
- Yellow nail syndrome (associated with pleural effusion – exudates).

**NB:** Amyloidosis does not cause bronchiectasis per se, but may be seen in bronchiectasis as a consequence of chronic inflammation and infection.

#### **Most common organisms isolated from patients with bronchiectasis:**

- Haemophilus influenzae (most common)
- Pseudomonas aeruginosa
- Klebsiella spp.
- Streptococcus pneumoniae

Bronchiectasis >>>> most common organism >>>> Haemophilus influenzae
--

#### **Management:**

- Postural drainage: is the cornerstone to treating bronchiectasis and should be undertaken at least once per day and more frequently during exacerbations.
- Physical training (e.g. inspiratory muscle training) - has a good evidence base for patients with non-cystic fibrosis bronchiectasis
- Antibiotics for exacerbations + long-term rotating antibiotics in severe cases

- Bronchodilators in selected cases
- Immunisations
- **Surgery** in selected cases (e.g. **Localised** disease) when underlying causes such as primary ciliary dyskinesia have been excluded.

Inhaled corticosteroids (**ICS**) should **not** be used routinely in bronchiectasis until further evidence of their effect on lung function and exacerbation frequency is available.

Symptom control in non-CF bronchiectasis >>> Inspiratory muscle training + postural drainage

### **Kartagener's syndrome (Immotile cilia syndrome)**

Kartagener's syndrome; also known as **primary ciliary dyskinesia (PCD)** and **immotile cilia syndrome** was first described in 1933 and most frequently occurs in examinations due to its association with dextrocardia in 50% of cases (e.g. 'quiet heart sounds', 'small volume complexes in lateral leads').

It is an inherited condition as an **autosomal recessive** disorder where the cilia lining the airways fail to function or function ineffectively due to a defect in the dynein molecule.

Features:

- 1) **Dextrocardia** (in **50%** of cases), or complete situs inversus totalis.
- 2) **Bronchiectasis**
- 3) **Recurrent sinusitis**
- 4) **Subfertility** (secondary to diminished sperm motility and defective ciliary action in the fallopian tubes)

Other associated conditions of immotile cilia syndrome are: Congenital heart defects, Deafness and Hydrocephalus.

### **Cystic fibrosis (CF)**

#### **Basics:**

- It is **autosomal recessive** disorder causing ↑ viscosity of secretions e.g. lungs and pancreas.

- It is due to defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which codes a cAMP – regulated chloride channel found in secretory epithelia.
- The airways become obstructed by thick mucus due to **defective chloride secretion** and **increased sodium resorption** across the airway epithelium. This leads to **bacterial colonisation** early in life with recurrent chest infection and bronchiectasis (**obstructive** lung disease by spirometry).
- The most common inherited lethal condition in Caucasians.
- In the UK 80% of CF cases are due to a deletion at delta F508 (**DF508 mutation**) on the long arm of chromosome 7.
- CF affects **1 per 2500** births, and the **carrier rate is 1 in 25**.
- Patients have **dry protein-rich secretions** which lead to complications of the pulmonary and gastrointestinal systems.
- CF is **the commonest cause of exocrine pancreatic insufficiency**.
- The disease presents with failure to thrive, steatorrhoea and abdominal pain. Diabetes mellitus can occur.

### Presenting features:

- 1) Neonatal period (around 20%): meconium ileus, less commonly prolonged jaundice.
- 2) Failure to thrive
- 3) Recurrent chest infections (40%)
- 4) GIT: malabsorption (30%): steatorrhoea, liver disease (10%), cholesterol gall stones (10-30%), peptic ulcers, ↑ GI malignancy, Constipation (dt defective CL secretion and ↑ Na absorption in the gut).
- 5) Pan-opacification of the nasal sinuses to be present in all CF patients

**Constipation** is common in patients with CF.

20 % have a fatty liver and gallstones are seen in 15% of young adults with the disease. Patients may also develop secondary biliary cirrhosis with mucus plugging of bile ducts and portal hypertension.

**Abdominal pain** with **cystic fibrosis** is due to **distal intestinal obstruction syndrome** (NOT by meconium ileus): occurs in 10-20% of patients with CF and incidence increases with age. About 80% of cases present for the first time in adults.

**Other features of cystic fibrosis:**

- **Delayed development and puberty** (Almost **100%** of children)
- **Short stature**
- **Pancreatic insufficiency** is very common, **85%** of patients affected. So defective absorption of fat-soluble vitamins like AKED.
- **Diabetes Mellitus** (occurs in **>65%** of patients by age 25 and this is **independent** of weight gain).
- **Nasal polyps** 15-20% (most of these occurring in the 2nd decade).
- **Rectal prolapse** is usually **idiopathic**, occurring between 1 - 5 years (due to bulky stools). Following defecation the prolapse usually **resolves spontaneously**, or through manual reinsertion by the patient or parent.
- **Male infertility** (occurs in 98% of adult men, it is due to **mal-development of the vas deferens** or to other forms of **obstructive azoospermia**).
- **Female subfertility** (due to **viscid** cervical secretions).

Female patient with CF, **after treating the acute infection she has a good chance of a successful pregnancy.**

But observational studies suggest that patient with **FEV1 less than 60%** of that **predicted** have a much worse outcome both with respect to their own health status and the viability of the pregnancy, and that chronic pseudomonas infection and multiple exacerbations do much worse. ☹

**Organisms which may colonise CF pts.:**

- It depends on the **age** of the patient:
  - Infants and young children become colonised by **Staphylococcus aureus** and then **Haemophilus influenzae**.
  - In teenagers, **Pseudomonas aeruginosa** colonisation occurs.
- **Pseudomonas aeruginosa >>> TTT Inhaled Tobramycin**
- **Aspergillus.**
- **Burkholderia cepacia.** (previously called: Pseudomonas cepacia)
- Mycobacterium tuberculosis, other mycobacteria

Sputum samples should be obtained, and organism identification and sensitivities can be used to guide treatment of future exacerbations.

**EX:** A 17-year-old girl with known cystic fibrosis presents with a chest infection. What antibiotic would be most suitable for her >>> the usual combination is **ceftazidime** and **tobramycin**, for a period of **2 weeks**.

Gentamicin can be used in place of tobramycin, but has poorer pseudomonal cover and is associated with significant side effects (nephrotoxicity and ototoxicity).

**Cepacia Syndrome in CF:**

Rapidly progressive fever, ↑ volume of purulent sputum, uncontrolled bronchopneumonia, septicaemia, weight loss, and poor outcome.

Approximately 3% of CF patients are thought to be colonized with cepacia (*Burkholderia cepacia*).

TTT:

\* **Ceftazidime + Aminoglycosides**

**Diagnosis:**

**Sweat test:** 2 reliable positive results on 2 separate days is diagnostic for CF. It is positive when **sweat chloride is more than > 60 mmol/L.**

The sweat test is conducted using **pilocarpine** iontophoresis.

A 3 mA current carries pilocarpine into the **skin of the forearm** stimulating local sweating. The arm is washed with distilled water and sweat collected on a filter paper or gauze. The **duration of collection is usually 30-60 minutes**. The filter paper is removed, weighed and eluted in distilled water.

**At least 50 mg and preferably 100 mg of sweat** should be collected for reliable results. It may not be possible to collect this amount in young infants.

**More than 60 mmol/L of chloride is diagnostic of CF** when one or more other criteria are present.

In healthy adults, the sweat chloride values increase slightly, but 60 mmol/L still differentiates CF from other conditions.

**False negative** results may be encountered in **nephrotic** syndromes.

Diagnosis of cystic fibrosis is usually clinical based on the **pulmonary** and **gastrointestinal** manifestations, family history and a positive sweat test. Confirmation is with genetic studies.

**Management of cystic fibrosis involves a multidisciplinary approach:**

- Regular (at least twice daily) chest physiotherapy and postural drainage. Parents are usually taught to do this. Deep breathing exercises are also useful
- **High calorie** diet, including **high fat** intake ( this is now the standard recommendation - previously high calorie, low-fat diets have been recommended to reduce the amount of steatorrhoea)
- Vitamin supplementation as Vit. D
- Pancreatic enzyme supplements taken with meals, they are required to help patients maintain weight.
- N-Acetylcysteine can be used in moderate episodes. This loosens and softens the plugs, presumably by 'opening' the disulphide bonds in the abnormal intestinal mucus and maintains luminal patency. Also N-Acetylcysteine can be put down the NG tube in I.O.
- Heart and lung transplant
- Gene therapy remains the ultimate goal for treatment.
- **Human recombinant DNase** given as a **single daily aerosol** seems to improve pulmonary function, decrease the frequency of chest exacerbations, and promotes a sense of well-being in patients with mild to moderate disease with purulent secretions. This may be because, in the inflamed airway, the nuclei from dead cells account for much of the viscosity of secretions.

Median survival has increased significantly over the past 10 years, and is now around **37 years** and is currently improving.

EX: A 25-year-old man who is known to have **DM** and suffers from **recurrent chest infections** is referred to the gastroenterology team with **chronic diarrhoea**. He has had **persistently abnormal liver function tests** over the last 3 months and an abdominal ultrasound scan showed a fatty liver and **gallstones**.

The most likely diagnosis is **Cystic fibrosis (CF)**



**Yellow nail syndrome (see pic)**

The **nails** are yellow, thickened, curved, stop growing and may become detached from the nail bed.

It is characterised by the triad of **yellow discolouration of the nails**, **lymphedema** and **pleural effusions**.

Associated findings include **bronchiectasis in 40% of cases**.

**Lung fibrosis**

Fibrosis predominately affecting the **upper** zones

- 1) Extrinsic allergic alveolitis (EAA)
- 2) **Coal** worker's pneumoconiosis/progressive massive fibrosis
- 3) Tuberculosis
- 4) **Sarcoidosis**
- 5) Histiocytosis
- 6) **Silicosis**
- 7) **Ankylosing spondylitis** (rare)
- 8) **Radiation**

Fibrosis predominately affecting the **lower** zones

- 1) Cryptogenic fibrosing alveolitis (IPF)
- 2) Most connective tissue disorders (**except** ankylosing spondylitis)
- 3) Drug-induced: (see later).
- 4) Asbestosis

It should be noted that the more common causes (cryptogenic fibrosing alveolitis, drugs) tend to affect the **lower** zones

**Histiocytosis X**: there is **pentalaminar X bodies** (Birbeck granules) found on **BAL** are considered diagnostic of pulmonary histiocytosis X.

The drugs which can classically cause pulmonary fibrosis include:

- Cytotoxics: like: **Methotrexate** , **Cyclophosphamide**, **Bleomycin**, Busulphan
- Antibiotics: e.g. **Nitrofurantoin**.
- Cardiac drugs: **Amiodarone**, **Hydralazine**, tocainide.
- Opiates: e.g. **Heroin** abuse
- **Sulphasalazine pulmonary toxicity** is rare, but is increasingly recognised.
- **Gold**
- **Dosulepin (Prothiadine ®)** (TCA) is recognised as a very **rare** cause of pulmonary fibrosis.

TTT: Drug withdrawal ± corticosteroids.

Penicillamine can be used in the treatment of pulmonary fibrosis.
---

### **Extrinsic allergic alveolitis (EAA) (Farmer lung) (HP)**

Extrinsic allergic alveolitis (EAA, also known as **hypersensitivity pneumonitis**) (**HP**) is a condition caused by hypersensitivity induced lung damage due to a variety of inhaled organic particles.

It is thought to be largely caused by immune-complex mediated tissue damage (type **III** hypersensitivity) especially in **acute** phase, although delayed hypersensitivity (type **IV**) is also thought to play a role, especially in the **chronic** phase.

It is now very rare since the majority of farmers no longer bale hay in wet conditions. When present, it is most commonly associated **with positive Saccharopolyspora rectivirgula antibodies**.

#### **Examples:**

- Pigeon **Bird** fanciers' lung: **avian** proteins
- **Farmers'** lung: spores of **Saccharopolyspora rectivirgula** (formerly Micropolyspora faeni) (NB: **Contaminated hay / straw** is the most common source of Saccharopolyspora rectivirgula which is responsible for Farmer's lung).
- **Malt** workers' lung: **Aspergillus clavatus**
- **Mushroom** workers' lung: thermophilic actinomycetes\*
- Mouldy hay, mushroom compost, house dust, **hot/tub steam room** and contaminated water in the humidifiers.

Acute episodes are characterised by neutrophilic infiltration followed by lymphocytic infiltration and raised levels of interleukins 1 and 8 and TNF-alpha. This results in direct cellular damage and increased vascular permeability, which results in hypoxia and reduced lung compliance. Prolonged exposure leads to fibrosis and parenchymal destruction.

### Presentation:

- Occur **4-8 hrs** after exposure, SOB, dry cough, fever.
- O/E: **Bilateral basal fine inspiratory crackles**

### Investigation:

- CXR: **Upper zone fibrosis**
- BAL: lymphocytosis
- Blood: **NO eosinophilia**
- Circulating **IgG precipitant**: In farmer's lung >>> precipitins to *Saccharopolyspora rectivirgula* or *Thermoactinomyces vulgaris* are found in 75-100% of cases during an acute episode.

#### **EAA >>> NOT ALLERGY:**

- NO Eosinophilia
- NO ↑ IgE
- NO positive skin prick
- NO Antibiotics

Positive serum avian **IgG** precipitins are **not diagnostic** of extrinsic allergic alveolitis (EAA), and only suggest the patient has had **old** exposure to birds.

### TTT:

- 1) Primary treatment is **antigen avoidance** (change of job, repainting and ventilation in the steam room) , Then,
- 2) **Systemic corticosteroids (Oral prednisolone)**. Inhaled corticosteroids (ICS) are not as effective as oral corticosteroids.
- 3) **NO** role for antibiotic therapy.

Although the aetiology is hypersensitivity to fungal spores, neither amphotericin B nor fluconazole are effective in the treatment of farmer's lung.

\*here the terminology is slightly confusing as thermophilic actinomycetes is an umbrella term covering strains such as *Micropolyspora faeni*.

### **Psittacosis** =

**Chlamydia psittaci pneumonia** is endemic in **birds including** psittacine birds, canaries, finches, pigeons and poultry.

Pet owners, vets and zoo keepers are most at risk.

It is **rare** in **children**.

**Person to person transmission** occurs especially in a hospital environment.

**Sputum** Gram stain reveals a **few** leucocytes and no predominant bacteria. There are few signs and few laboratory/x ray findings.

It is characterized by **relative bradycardia** with non-specific chest signs, coupled with diffuse CXR changes like widespread hazy opacities affecting both **lower** lobes, a **low TLC** and **abnormal LFTs** are consistent with the disease.

Positive serology is with complement-fixing antibodies.

**Serum avian precipitins** is **positive**.

**Tetracyclines** are the antibiotics of choice.

### Idiopathic pulmonary fibrosis (IPF)

Idiopathic pulmonary fibrosis, (previously termed cryptogenic fibrosing alveolitis), is a chronic lung condition characterised by progressive fibrosis of the interstitium of the lungs.

Whilst there are many causes of lung fibrosis (secondary fibrosing alveolitis) (e.g. medications, connective tissue disease, SLE, sarcoidosis, asbestos, pneumoconiosis).

However, the term IPF is reserved when no underlying cause exists.

IPF is typically seen in patients aged **50-70 years** and is twice as common in **men**.

Features:

- **Progressive exertional dyspnoea**
- **Bilateral fine basal crackles** on auscultation
- **Clubbing**
- Dry cough
- PFT shows **restrictive** lung spirometry with the reduced TLCO and KCO.

There are **no satisfactory treatment options** for **idiopathic pulmonary fibrosis (IPF) = (Usual Interstitial Pneumonia (UIP))**.

It is necessary to distinguish UIP from non-specific interstitial pneumonia (NSIP) as this is more steroid-responsive.

HRCT chest is very important for differentiating UIP from NSIP.

**Bronchoalveolar lavage (BAL) lymphocytosis** predicts a **better corticosteroid response** than the typical BAL neutrophilia.

**Diagnosis:**

- 1) Spirometry: classically a restrictive picture (FEV1 normal/decreased, FVC decreased, FEV1/FVC increased).
- 2) Impaired gas exchange: reduced transfer factor (TLCO).
- 3) CXR: bilateral interstitial shadowing (typically small, irregular, peripheral opacities - 'ground-glass' in lower zones - later progressing to 'honeycombing').
- 4) **HRCT**: High-resolution CT scanning is the investigation of choice and required to make a diagnosis of IPF
  - a. A predominant **reticular** pattern on HRCT is consistent with UIP and correlates with irreversible fibrosis.
  - b. The **ground glass** appearance often associated with NSIP indicates inflammation, which may be responsive to steroids.
- 5) ANA positive in 30%, RF positive in 10% but this does not necessarily mean that the fibrosis is secondary to a connective tissue disease. Titres are usually low

**Management:**

- Pulmonary rehabilitation
- Supplementary **oxygen (LTOT)**.
- Lung transplantation.
- There is some evidence that pirfenidone (an anti-fibrotic agent) may be useful in selected patients.
- Other options under clinical trials include interferon-gamma 1beta and Bosentan.
- Unfortunately responsiveness to corticosteroids in idiopathic pulmonary fibrosis is **poor**, although up to **20%** may show some objective response with respect to stabilisation of lung function. Whilst only 20% of patients may be steroid responsive, other treatments include azathioprine and cyclophosphamide.

The chance for IPF of this being responsive to corticosteroids is **1:5** which depends on **Bronchoalveolar lavage BAL lymphocytosis**.

**Prognosis:**

- Poor, average life expectancy is around 3-4 years

**EX:** A male patient about 55 years old has recently been diagnosed with **idiopathic pulmonary fibrosis**, he wants to know if he is suitable for steroid therapy >> It depends on **BAL lymphocytosis >> good steroid response**.

### **Lymphoid interstitial pneumonia**

- C/P: **gradual onset breathlessness over** considerable time about 2 years, **intermittent fevers, weight loss** and **inspiratory crackles**.
- There is mild **anaemia** and **high immunoglobulins**.
- CXR: diffuse **lower zone alveolar shadowing**.
- Lung Biopsy: diffuse **lymphoid interstitial infiltrates**.
- PFT: **restrictive** pattern.
- It is usually associated with **HIV (IV drug abusers)**, **connective** tissue disease, **HBV** infection, chronic active hepatitis and **Hashimoto's thyroiditis**.

### **Sarcoidosis**

- Sarcoidosis is a **multisystem** disorder of unknown aetiology characterised by **non-caseating granulomas**.
- It is more common in young adults and in people of **African** descent.
- Prevalence varies amongst different ethnic populations; in Europe, sarcoid is commonest amongst **Caucasians** and has a significantly higher incidence in the **Irish**.
- This non-caseating granulomas may occur **anywhere**.
- These granulomas have the capacity to produce **1, 25 vitamin D** explaining the associated hypercalcaemia.
- This has a **good prognosis** and usually **resolves spontaneously** over 6 to 8 weeks.
- However, **TB should be excluded** by sending sputum or BAL washings for AFB.
- The tuberculin test is negative in approximately 80-90 % of sarcoidosis cases, but its rule in diagnosis is controversial.
- Inflammatory **arthritis** in sarcoidosis typically targets the **ankle** joint.

**Sarcoidosis remits without treatment in approximately two-thirds of people.**

**There is no one diagnostic test for sarcoidosis** and hence diagnosis is still largely clinical.

- Investigations:

#### **1) HRCT chest:**

- It can demonstrate the degree of fibrosis, micronodules in a subpleural or bronchoalveolar distribution, fissural nodularity and bronchial distortion.
- Irregular linear opacities and ground-glass shadowing may also be seen.
- If the CT scan is diagnostic, then mediastinoscopy, bronchoscopy or biopsies can often be avoided.

2) **Trans-bronchial biopsy** (Tissue biopsy): It is the **definitive route to confirming the diagnosis** and positive results are seen in **90%** of cases showing **non-caseating granulomas**.

➤ **Other investigations:**

- **Chest x ray** which is abnormal in 90% of lung sarcoidosis, but 30-60% are asymptomatic (that is, incidental CXR finding). So sarcoidosis is often picked up on routine CXR.
- **ACE levels:**
  - It is elevated in about 70% of patients with active sarcoidosis.
  - It have a sensitivity of 60% and specificity of 70% and are therefore not reliable in the diagnosis of sarcoidosis.
  - It is not a diagnostic test.
  - It is best used to assess the response of steroid therapy.
  - It have a role in monitoring disease activity as it reflects macrophages activity.
  - It is not specific as it can be elevated in patients with histoplasmosis, Miliary TB, Gaucher's, lymphoma or, hepatitis, liver diseases (as in liver disease, slow the metabolic excretion of serum ACE and so increased ACE activity).
  - A normal serum ACE would not exclude the diagnosis.
  - Increased ACE in CSF may be useful in diagnosis of CNS sarcoidosis.
  - Tissue ACE activity is highest in sarcoid LN rather than in pulmonary tissues.
- Routine bloods may show hypercalcaemia (seen in 10% of patients) and it is due to overproduction of vitamin D by sarcoid granulomas and a raised ESR.

- Leukopenia in 5-10% of patients.
- Hypergammaglobulinaemia (↑ Immunoglobulins) in 30-80%.
- Spirometry: may show a restrictive defect, decreased compliance and impaired diffusion capacity.
- Gallium-67 scan - not used routinely
- The Kveim test (where part of the spleen or LN extracts from a patient with known sarcoidosis is injected under the skin) with a granulomatous reaction appearing 4 weeks after intradermal injection, which is no longer performed due to concerns about cross-infection, it is positive in 50-60% of patients.
- Cardiac sarcoidosis is rare but can manifest as a prolonged PR interval.

**A CXR may show the following changes:**

- Stage 0 = normal
- Stage 1 = Bilateral hilar lymphadenopathy (BHL)
- Stage 2 = BHL + interstitial infiltrates
- Stage 3 = Diffuse interstitial infiltrates only
- Stage 4 = Diffuse fibrosis

**Sarcoidosis CXR**

- 1 = BHL
- 2 = BHL + infiltrates
- 3 = Infiltrates only
- 4 = Fibrosis

**TTT:**

- **Prednisolone** is the mainstay of initial treatment for sarcoidosis, continued **for 12 months** or more in those patients who respond, but tapered to the minimal effective dose to stop within 2 years maximum.
- Most patients achieve remission within 2 years.
- Methotrexate and hydroxychloroquine may be added as steroid sparing agents.



### Indications for steroids ttt:

- Hypercalcaemia.
- Worsening lung function.
- Eye (bilateral posterior uveitis is common eye manifestation)
- Heart or neuro involvement.

### Prognostic features:

Factors associated with **poor prognosis**Ⓢ

- Age of onset >40 years
- Insidious onset, symptoms > 6 months
- Absence of erythema nodosum
- Extra pulmonary manifestations: e.g. splenomegaly, **lupus pernio** (is a chronic raised purplish indurated hard lesion of the skin)
- CXR: stage III-IV features
- **Black** people (**Afro**-Caribbean or **Afro**-American race)
- Cardiac involvement
- Neuro-sarcoidosis
- Chronic hypercalcaemia
- Nasal mucosal involvement

Erythema nodosum is associated with a good prognosis in sarcoidosis

### **Mikulicz syndrome:**

It is a chronic condition characterized by the abnormal enlargement of parotids, lacrimal and salivary glands. The tonsils and other glands in the soft tissue of the face and neck may also be involved. It is associated with sarcoidosis.

### **Lofgren's syndrome**

- Lofgren's syndrome is an **benign acute form sarcoidosis** characterised by:
  - 1) Bilateral hilar lymphadenopathy (BHL),
  - 2) Erythema nodosum (EN),
  - 3) Fever
  - 4) Polyarthralgia.
- It typically occurs in young females and carries an excellent prognosis and the development of chronic disease is rare.
- So if you suspect, **follow up** appointment with **CXR** in **3** months.

NB: **Löffler's syndrome** is a cause of pulmonary **eosinophilia** with **bronchospasm**, **abdominal** discomfort and **urticarial rash** thought to be caused by parasites such as Ascaris lumbricoides, Strongyloides.

**Heerfordt's syndrome** is an **acute** presentation of sarcoidosis, which presents with **fever**, **uveitis** (red, painful eyes), **bilateral** swelling of the **parotid** and **other salivary and lacrimal glands**. **Facial nerve palsy (LMNL)** may be a feature, and other features of sarcoidosis may co-exist (e.g. skin lesions, pulmonary involvement).

As it represents a form of **neuro-sarcoidosis**, other neurological features may be present (e.g. meningism, ophthalmoplegia and pupillary reflex dysfunction).

### **Bilateral hilar lymphadenopathy (BHL)**

The most common causes of bilateral hilar lymphadenopathy (BHL) (Bulky mediastinum) are **Sarcoidosis** and **Tuberculosis**.

Other causes include:

- Lymphoma/other malignancy.
- Pneumoconiosis e.g. Berylliosis
- Fungi e.g. histoplasmosis, coccidioidomycosis

NB: Amyloidosis is not commonly associated with bilateral hilar lymphadenopathy

### **Pneumoconiosis**

Pneumoconiosis is a chronic reaction of the lung parenchyma as a consequence of **chronic dust inhalation**

**Pneumoconiosis is an x ray diagnosis.**

Typical CXR appearance of the different dust particles are listed below:

Coal	Multiple small round opacities, typically 1–10 mm in diameter, mostly in the upper lobes
Asbestos	Pleural plaques and fibrosis more marked in the lower zones
Silica	Multiple small nodules scattered diffusely throughout the lungs and egg-shell calcification of the hilar nodes
Beryllium	Acute pneumonitis that may continue to a granulomatous reaction (compare with sarcoidosis) with lymphadenopathy
Iron dust	Nodular pulmonary pattern with greater density but with less marked fibrosis

### **Berylliosis**

Exposure to **beryllium** is seen in the **nuclear** power, **telecommunications**, semi-conductor and **electronics** industries. مهندس اليكترونيات وذرات

It results in a similar clinical picture to that of **sarcoidosis**.

The lung histology shows **non-caseating granulomatosis**.

**EX:** A 53-year-old man presents to the respiratory clinic. He has been involved in **nuclear power plant construction** for much of his life and has increasing shortness of breath and chronic cough over the past 12 months.

CXR shows bilateral hilar lymphadenopathy.

Which of the following is the most likely diagnosis? >>> **Berylliosis**

In this case it is the patient's occupation that pushes us towards berylliosis as the most appropriate answer.

Sarcoidosis is the major differential here, but it is the possible exposure to beryllium because of occupation which points us away from this as the most likely diagnosis.

### **Silicosis**

**Silicosis is a risk factor for developing TB** (silica is toxic to macrophages).

Silicosis is a fibrotic lung disease associated with the inhalation of silicon dioxide (silica). It is usually found in quarry workers or miners and also sandblasters, pottery workers and stone masons (if the dust contains quartz).

Features:

- Fibrosing lung disease (**UPPER** zone).
- The pathognomic radiological changes: 'egg-shell' calcification of the hilar lymph nodes.

Diagnosis of silicosis is made on industrial history and typical CXR changes.

### **Asbestos and the lung**

Asbestos can cause a variety of lung disease from benign pleural plaques to mesothelioma:

#### **Pleural plaques:**

Pleural plaques are **benign** and do not undergo malignant change.

They are the most common form of asbestos related lung disease and generally occur after a latent period of 20-40 years.

It does not become apparent until 20 years or more after exposure.

Pleural plaques are not precursors of malignant change, but they reflect previous asbestos exposure.

### **Pleural thickening:**

Asbestos exposure may cause diffuse pleural thickening in a similar pattern to that seen following an empyema or haemothorax.

### **Asbestosis:**

The severity of asbestosis is related to the length of exposure (as in working in the **boiler** industry, **plumber**).

The latent period is typically 15-30 years. The onset of asbestosis is typically over 20 years following exposure.

Asbestosis typically causes **lower** lobe fibrosis.

**Pleural effusions / thickening** may result from **acute** asbestos pleurisy.

As with other forms of lung fibrosis the most common symptoms are shortness-of-breath and reduced exercise tolerance.

There is no specific treatment for asbestosis. Further exposure should be avoided, and patients should be vaccinated against pneumococcus and influenza. Patients should be advised to stop smoking (if they do) and long-term oxygen therapy (LTOT) may be required.

### **Mesothelioma:**

Mesothelioma is a **malignant** disease of the pleura.

There are 3 types of asbestos: blue, brown and white.

Crocidolite (blue) and brown asbestos is the most dangerous form.

Mesothelioma does not usually develop until 10-50 years after exposure to asbestos and for this reason it is often difficult to discover the exact cause.

Rarely, mesothelioma develops in people who have never exposed to asbestos.

Significant previous radiation exposure has also a significant aetiology in some cases of malignant mesothelioma.

Research has not found any evidence that smoking increases a person's risk of developing mesothelioma, also exposure to other building materials such as fiberglass does not increase the risk.

Possible features:

- Progressive shortness-of-breath
- Chest pain
- Pleural effusion

If suspect Mesothelioma >>> **Thoracoscopy** with **drainage** and **biopsy**.

### **Diagnosis of mesothelioma is by Thoracoscopy and biopsy**

Tissue can be obtained from thoracoscopy with biopsy from abnormal looking areas, as such this is **the most appropriate investigation** to deliver the diagnosis.

Blind pleural biopsy may result in tissue being obtained from an area not affected by mesothelioma. As such this is not correct.

Whilst thoracentesis is likely to obtain malignant cells, the histopathologist may not be able to type them adequately.

CT scanning may reveal structural abnormalities but will not give a histological diagnosis and sputum cytology would be unlikely to reveal malignant cells.

Pleural effusion in mesothelioma tends to have normal LDH and < 1000 WBCs /ml.

But if the effusion has **less glucose, high protein** with ↑ WBCs mainly **lymphocytes** >>> so think of **tuberculous effusion**

Patients are usually offered palliative chemotherapy and there is also a limited role for surgery and radiotherapy.

Unfortunately the prognosis is very poor, with a median survival from diagnosis of 8-14 months.

### **Lung cancer:**

Asbestos exposure is a risk factor for lung cancer and also has a synergistic effect with cigarette smoke.

## Pulmonary embolism (PE)

### NICE guidelines

All patients with symptoms or signs suggestive of a PE should have a history taken, examination performed and a chest x-ray to exclude other pathology.

If a PE is still suspected a two-level PE **Wells score** should be performed:

Clinical feature	Points
<b>Clinical</b> signs and symptoms of DVT (minimum of <b>leg</b> swelling and pain with palpation of the deep veins)	<b>3</b>
An alternative diagnosis is less likely than PE ( <b>PE</b> is #1 diagnosis, or equally likely)	<b>3</b>
<b>HR</b> > 100 /min	<b>1.5</b>
<b>Immobilisation</b> for more than <u>3 days</u> or <b>surgery</b> in the previous <u>4 weeks</u>	<b>1.5</b>
<b>Previous</b> DVT/PE	<b>1.5</b>
<b>Haemoptysis</b>	<b>1</b>
<b>Malignancy</b> (on treatment, treated in the last 6 months, or palliative)	<b>1</b>

It is important to note the **minor and major risk factors** for PE/VTE (BTS):

Minor risk factors (with a relative risk of 2-4)	Major risk factors (relative risk 5-20)
<ul style="list-style-type: none"> <li>• <b>Oral contraceptive pill</b></li> <li>• Occult malignancy</li> <li>• Long distance travel</li> <li>• Thrombotic disorder.</li> <li>• HTN</li> <li>• CHF</li> </ul>	<ul style="list-style-type: none"> <li>• Lower limb problems including a <b>fracture</b> or <b>varicose veins</b>.</li> <li>• Post-operative ICU stay.</li> <li>• Abdominal/pelvic or advanced <b>malignancy</b></li> <li>• <b>Previous VTE</b>, and</li> <li>• <b>Pregnancy</b>.</li> </ul>

**Traditional interpretation:**

- High score: >6.0
- Moderate score: 2.0 to 6.0
- Low score: <2.0

**Clinical probability simplified scores**

- PE **likely**: (> 4): more than 4 points >>> Consider diagnostic imaging.
- PE **unlikely**: ( $\leq 4$ ): 4 points or less >>> Consider D-dimer to R/O PE.

If a PE is 'likely' (more than 4 points) arrange an immediate computed tomography pulmonary angiogram (CTPA). If there is a delay in getting the CTPA then give LMWH until the scan is performed.

If a PE is 'unlikely' (4 points or less) arrange a D-dimer test. If this is positive arrange an immediate computed tomography pulmonary angiogram (CTPA). If there is a delay in getting the CTPA then give LMWH until the scan is performed.

If the patient has an allergy to contrast media or renal impairment a V/Q scan should be used instead of a CTPA.

PE >>>> tachycardia, tachypnea, low grade fever with normal CXR.

**D-dimers:**

- **Sensitivity = 95-98%, but poor specificity**
- **It is good -ve test** (i.e. if -ve >>> so exclude PE, if +ve >>> not specific for PE may be due to other causes rather than PE) (already high in pregnancy>>>useless).
- Most D-dimer assays have a **high negative predictive value (NPV)** (approximately 90%). (NPV is the probability that the patient does not have the disease given a negative test result, that is, if the test is negative they are unlikely to have the disease.)
- However the positive predictive value (PPV) is often low (approximately 15%). (PPV is the probability that the patient will have a condition given a positive test result, that is, in the case of D-dimer a positive result does not correlate with a high probability of disease). The test is therefore **useful to exclude DVT rather than to confirm DVT**.
- Current evidence strongly supports the use of a D-dimer assay in the clinical algorithm of suspected DVT. In other words, the clinical likelihood of a DVT should be taken into account when interpreting the results of the D-dimer assay.

**ECG:**

- The classic ECG changes seen in PE are a large S wave in lead I, a large Q wave in lead III and an inverted T wave in lead III - '**S1Q3T3**'. However this change is seen in no more than **20%** of patients.
- RBBB and right axis deviation are also associated with PE.
- **Sinus tachycardia** may also be seen.

**V/Q scan:**

- **Xenon** is used for imaging **ventilation**, whilst technetium labelled macroaggregated human serum albumin (**MAA**) is used to image **perfusion**.
- No use of iodine so it is not contraindicated in iodine hypersensitivity.
- **Sensitivity = 98%; but a specificity = 40%** - high negative predictive value, i.e. **if normal perfusion virtually excludes PE**
- Other causes of mismatch in V/Q include old pulmonary embolisms, AV malformations, vasculitis, and previous radiotherapy.
- COPD gives matched defects.
- In mitral valve disease >> Increased pulmonary venous pressure >> increased perfusion flow to the upper lobes.
- Radiation to the foetus is small. It is **not contraindicated in pregnancy**, although the perfusion only scan is adequate.
- V/Q scanning carries a slightly increased risk of **childhood cancer** compared with CTPA (1/280,000 versus less than 1/1,000,000).

**CTPA:**

- Peripheral emboli affecting subsegmental arteries may be missed

**Pulmonary angiography:**

- The gold standard
- Significant complication rate compared to other investigations



**CTPA or V/Q scans?**

The British Thoracic Society (BTS) published guidelines back in 2003 on the management of patients with suspected pulmonary embolism (PE). Key points from the guidelines include:

- Computed tomographic pulmonary angiography (**CTPA**) **is now the recommended initial lung-imaging modality for non-massive PE.**

Pulmonary embolism >>>> <b>CTPA is first-line investigation</b>
---

- Advantages compared to V/Q scans include speed, easier to perform out-of-hours, a reduced need for further imaging and the possibility of providing an alternative diagnosis if PE is excluded.
- If the CTPA is negative then patients do not need further investigations or treatment for PE.
- V/Q scanning may be used initially if appropriate facilities exist, the chest x-ray is normal, and there is no significant symptomatic concurrent cardiopulmonary disease.
- It is still common in UK hospitals, despite guidelines, for a ventilation-perfusion scan to be done first-line.

**Pregnancy: DVT/PE investigation**

Guidelines were updated in 2010 by the Royal College of Obstetricians. Key points include:

- Chest x-ray should be performed in all patients (with abdominal shield).
- Compression duplex Doppler should be performed if the chest x-ray is normal - this may provide indirect evidence of a pulmonary embolism as both conditions require anticoagulation this may negate the need for further radiation exposure. But it does not exclude asymptomatic proximal venous thrombosis.
- D-dimer is of limited use in the investigation of thromboembolism as it often raised in pregnancy.
- Echocardiography may show acute right sided dilatation, but this is by no means diagnostic.
- The decision to perform a V/Q or CTPA should be taken at a local level after discussion with the patient and radiologist:

**Comparing CTPA to V/Q scanning in pregnancy:**

CTPA	V/Q scanning
CTPA slightly increases the lifetime risk of <b>maternal breast cancer</b> (increased by up to 13.6%, background risk of 1/200 for study population). <u>Pregnancy makes breast tissue particularly sensitive to the effects of radiation.</u>	V/Q scanning carries a slightly increased risk of <b>childhood cancer</b> compared with CTPA (1/280,000 versus less than 1/1,000,000)

In the **pregnancy** situation with probability of PE >>> **the optimal way to exclude PE** is >>> **Half dose V/Q scan.**

If **low** probability of PE >>> discharge and follow up

If **high** probability of PE >>> LMWH

Initially estimation of **pre-test probability** by senior staff

Then **D-Dimer**, if further investigation is needed, so

Then **CXR** is the next step in absence of leg signs.

If there is no leg signs, so progress to **CXR and CTPA** if clinical suspicious is very high.

But in the presence of leg signs, **bilateral leg Doppler US** can be performed.

If leg Doppler is positive, CXR then CTPA are the next recommended steps.

**Pulmonary embolism: management**

The NICE guidelines of 2012 provided some clarity on how long patients should be anticoagulated for after a pulmonary embolism (PE). Selected points are listed below.

Low molecular weight heparin (LMWH) or fondaparinux should be given initially after a PE is diagnosed.

An exception to this is for patients with a massive PE where thrombolysis is being considered. In such a situation unfractionated heparin should be used.

- A vitamin K antagonist (i.e. warfarin) should be given within 24 hours of the diagnosis.

- The LMWH or fondaparinux should be continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time with warfarin until the INR is in the therapeutic range
- Warfarin should be continued **for at least 3 months**. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'
- NICE advice extending warfarin **beyond 3 months for patients with unprovoked PE**. This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months. (i.e. Pt. with PE of no cause >>>> warfarin for 6 months). مش معروف السبب يبقى طول مدة العلاج
- For patients with active cancer NICE recommend using LMWH for 6 months.

Thrombolysis:

- Thrombolysis is now recommended as the first-line treatment for **massive PE where there is circulatory failure** (e.g. hypotension or arrest PEA). Other invasive approaches should be considered where appropriate facilities exist

Massive PE + cardiopulmonary arrest (PEA) >>>>> **IV thrombolysis**, then **followed by CPR for 90 minutes**.

**In acute major PE with low BP >>>**

- 1) **IV fluids** should be given firstly to increase RV filling pressure and maintain COP.
- 2) **Heparinisation** will prevent further emboli occurring.
- 3) If hypotension is severe and do not respond to plasma expanders, Use **inotropic** support.
- 4) **Thrombolysis** should be considered if the patient is not improving after 15-30 minutes with the above measures.
- 5) **Pulmonary embolectomy** should only be undertaken when thrombosis is contraindicated.

### **Pneumothorax**

The British Thoracic Society (BTS) published updated guidelines for the management of spontaneous pneumothorax in 2010.

A pneumothorax is termed primary if there is no underlying lung disease and secondary if there is (like asthma, COPD).

If Pt. has asthma >>>> ttt as secondary pneumothorax
--

**Primary pneumothorax:**

- If the rim of air is < 2cm and the patient is not short of breath then discharge should be considered and review in the clinic in 2 to 3 wks.
- Otherwise aspiration should be attempted.
- If this fails (defined as > 2 cm or still short of breath) then a chest drain should be inserted.
- If following aspiration the rim of air is < 2cm and the breathing has improved then discharge should be considered with outpatient review.

**Secondary pneumothorax:**

- If the patient is > 50 years old and the rim of air is > 2cm and/or the patient is short of breath then a chest drain should be inserted.
- Otherwise aspiration should be attempted if the rim of air is between 1-2cm. Even if successful the patient should be admitted and observed for at least 24 hours. If aspiration fails (i.e. pneumothorax is still greater than 1cm) a chest drain should be inserted. All patients should be admitted for at least 24 hours.
- If the pneumothorax is less the 1cm then the BTS guidelines suggest giving oxygen and admitting for 24 hours.
- **NB: Regarding scuba diving**, the BTS guidelines state: 'Diving should be permanently avoided unless the patient has undergone bilateral surgical pleurectomy and has normal lung function and chest CT scan postoperatively.'
- **NB: Air travel** is acceptable once the pneumothorax has fully resolved (Pt. can't air travel for 2 wk. post complete aspiration of the air).
- Unlike a primary pneumothorax, a secondary pneumothorax always requires intervention.
- It is preferable the insertion of a **small bore chest drain (8-14 SWG)** as there are no advantages in the insertion of a large bore chest drain (>20 FG) as it usually more painful and delays discharge.
- The most appropriate point for chest drain insertion is in **the 'safe triangle' in the mid-axillary line**. This reduces the chance of injury to the internal mammary artery, muscle, liver and spleen.

Atmospheric air drops during flights and increases in deep sea diving can cause recurrence of pneumothorax. This is due to expansion and rupture of pulmonary blebs. Many commercial airlines previously advised a **6-week** interval between pneumothorax and air travel, but this has now been amended to **1 week** following full resolution.

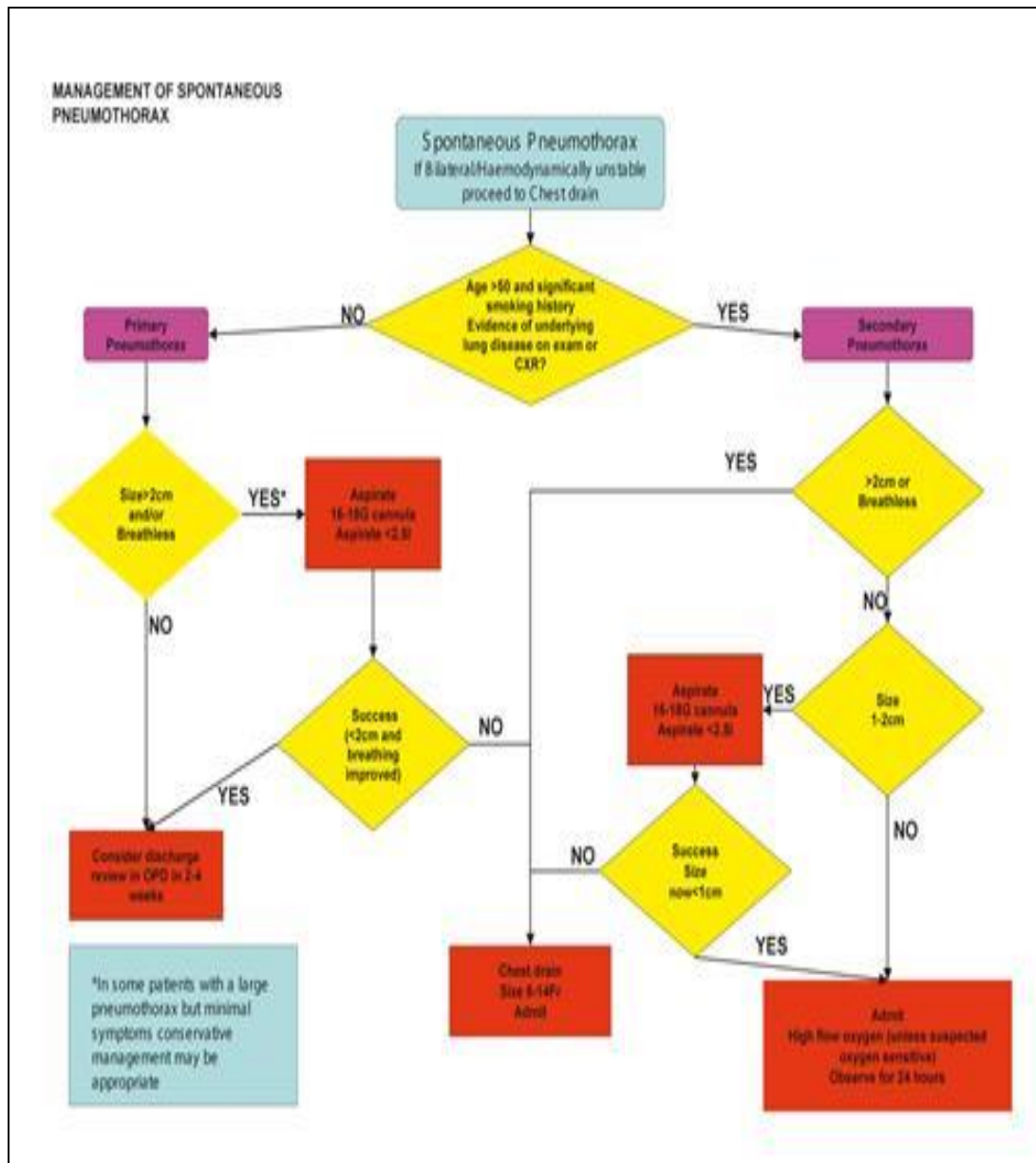
However, the British Thoracic Society emphasises that **the recurrence risk only significantly falls after 1 year**, and therefore in the absence of a definitive surgical procedure patients might wish to defer travel until then.

### Iatrogenic pneumothorax:

- Less likelihood of recurrence than spontaneous pneumothorax.
- Majority will resolve with observation, if treatment is required then aspiration should be used.
- Ventilated patients need chest drains, as may some patients with COPD.

**NB:** **Hamman's sign** (or '**crunch**') is a crunching **systolic** sound heard over the sternal edge in mediastinal emphysema or left apical pneumothoraces.

It can be dependent on the patient's position when auscultating.



**NB:** Questions sometimes discuss the size of the pneumothorax in **percentage** terms rather than giving the **interpleural distance**. A variety of formulas have been proposed to convert between the two.

As a very general rule of thumb:

Average interpleural distance	Approximate size of pneumothorax
0.5 cm	10%
1 cm	15 %
2 cm	30%

3 cm	45%
4 cm	60%

**EX.** A 1ry pneumothorax of 20% is therefore within the 2 cm limit >>> so for observation, if there is no shortness of breath.

The management of choice for a **second unilateral pneumothorax** in a **fit individual** is referral to a **thoracic surgeon for bullectomy and pleurectomy**, this is conducted under **VATS** (Video Assisted Thoracoscopic Surgery).

Until then, activities such as diving and flying are contraindicated.

**Pleurodesis** could be considered in **elderly** or **frail** individuals, but is not suitable in young fit patient.

As his lung has re-expanded after ICT, there will be no broncho-pleural fistula.

## VATS

Video Assisted Thoracoscopic Surgery is indicated in:

- 1) **Second time ipsilateral** pneumothorax
- 2) **Bilateral spontaneous** pneumothorax
- 3) **Spontaneous haemothorax**
- 4) **Persistent air leak** (more than 5 to 7 days of drainage)
- 5) Certain occupations, for example, pilots or divers.

## Pleural effusion: investigation

Imaging:

- Posterior-anterior (PA) chest x-rays should be performed in all patients
- Ultrasound is recommended by BTS: it increases the likelihood of successful pleural aspiration and is sensitive for detecting pleural fluid septations.

Pleural aspiration:

- As above, ultrasound is recommended to reduce the complication rate.

- A **21G** needle and 50ml syringe should be used.
- Fluid should be sent for pH, protein, lactate dehydrogenase (LDH), cytology and microbiology

**Exudate (> 30g/L protein):**

- Infection: pneumonia, TB, sub-phrenic abscess
- Connective tissue disease: RA, SLE
- Neoplasia: lung cancer, mesothelioma, metastases
- Pancreatitis
- Pulmonary embolism
- Dressler's syndrome
- Yellow nail syndrome: It is very rare, affects adults, also known as Primary lymphedema, It is pleural effusion associated with yellow dystrophic nails + bronchiectasis (in 40%), also associated with chronic sinusitis and persistent cough.

**Transudate (< 30g/L protein):**

- 1) Heart failure
- 2) Hypoalbuminaemia (liver disease, nephrotic syndrome, malabsorption)
- 3) Hypothyroidism
- 4) Meigs' syndrome (a triad of: Ascites+ Rt. pleural effusion + benign ovarian tumour fibroma). It resolves after the resection of the tumour.

**Light's criteria** was developed in 1972 to help distinguish between a transudate and an exudate. The BTS recommend using the criteria for borderline cases:

- Exudates have a protein level of >30 g/L,
- Transudates have a protein level of <30 g/L
- If the protein level is between 25-35 g/L, Light's criteria should be applied.
- An **exudate** is likely if at least one of the following criteria are met:
  - Pleural fluid protein divided by serum protein **>0.5**
  - Pleural fluid LDH divided by serum LDH **>0.6**
  - Pleural fluid LDH more than two-thirds the upper limits of normal serum LDH



**Raised LDH >>> Inflammatory exudate.**

Other characteristic pleural fluid findings:

- Low glucose: T.B, Rheumatoid arthritis
- Raised amylase: pancreatitis, oesophageal perforation
- Heavy blood staining: mesothelioma, pulmonary embolism, tuberculosis
- **Uniform blood staining** throughout pleural fluid samples: **Malignancy**
- **Low pleural PH less than 7.2 >>> Empyema**, inflammatory effusion related to RA, TB, malignancy and oesophageal rupture.

**The pleural glucose level is low:** Levels less than **3.3** mmol/L are found in:

- Empyema
- Tuberculosis
- Malignancy
- Rheumatoid arthritis
- Lupus
- Oesophageal rupture

In a unilateral pleural effusion, which in the clinical setting may represent an empyema.

It is therefore critical that you urgently obtain a **sample of pleural fluid** to confirm or exclude this, as an **empyema** requires a **chest drain** to be inserted. If pus is obtained, a chest drain should be inserted.

Other fluid should be tested for **pH**, and if **less than 7.2** this indicates an empyema and a drain should again be inserted.

Fluid should also be sent for **protein** and **LDH** (to determine if it is a **transudate** or **exudate**), glucose, gram stain, microscopy, culture and sensitivity and cytology.

Current UK best practice guidelines indicate US should be used to guide pleural aspiration, but US alone is unlikely to add further information.

Sputum cultures, whilst useful, will take at least 3-5 days to yield diagnostic information and pleural aspiration is therefore more critical at this stage.

**Unilateral pleural effusion >>> Diagnostic pleural fluid sampling ± drain, CT Thorax** should be considered to rule out tumours.

**NB:** Head and neck or oesophageal or cardiothoracic surgery (even neck LN excision) can cause **damage to thoracic duct**, which can lead to **chylous formation** (whitish milky pleural effusion) about 4 litres of fluids per day to leak into the pleural space, so large pleural effusion. To confirm the diagnosis, you can test the effusion for **lipase** or **triglycerides**.

**Pleural triglyceride level more than 1.2 mmol/l** >>> indicate a 99% chance that this is **chylous** pleural effusion.

### **Chest x-ray: cavitating lung lesion**

#### Differential

- 1) Tuberculosis
- 2) Fungal infections: Aspergillosis, Histoplasmosis, Coccidioidomycosis
- 3) Malignancy: Squamous cell lung cancer
- 4) Lung abscess (Staph aureus, Klebsiella and Pseudomonas)
- 5) Wegener's granulomatosis
- 6) Lung infarction: Pulmonary embolism
- 7) Rheumatoid arthritis

EX: Old pt. + **DM** + CXR: cavitating apical shadow >>> **TB** >>> **Sputum AFB**, If pt. unable to produce sputum >>> **bronchoscopy** + **BAL** for TB

EX: A 45-year-old **seaman** presents with cough and fever. A CXR demonstrates a **cavitating** lung lesion.

Which of the following is the most likely cause? >>> **Histoplasmosis**.

Histoplasmosis normally evolves slowly over as long as 20 years but may follow a more rapid course in the immunocompromised (seamen may be more prone to sexually transmitted diseases **STDs** such as **HIV**).

### **Lung cancer: types**

#### Background:

- It is well known that the incidence of adenocarcinoma is rising in comparison to the other types of non-small cell lung cancer.

Adenocarcinoma is now the most common type of lung cancer in the USA.

In the UK, Squamous cell cancer remains the most common subtype.

Lung cancer:

- **Squamous**: 35%
- Adenocarcinoma: 30%
- Small (oat) cell: 15%
- Large cell: 10%
- Other: 5%

Other tumours:

- Alveolar cell carcinoma: not related to smoking, ++sputum
- Bronchial adenoma: mostly carcinoid

### **Lung cancer: risk factors**

#### **1) Smoking**

- Increases risk of lung ca by a factor of 10

2) Other factors:

- Asbestos - increases risk of lung ca by a factor of 5
- Arsenic
- Radon
- Nickel
- Chromate
- Aromatic hydrocarbon
- Cryptogenic fibrosing alveolitis

Factors that are NOT related

- Coal dust

**NB**: Smoking and asbestos are synergistic, i.e. a smoker with asbestos exposure has a  $10 \times 5 = 50$  times increased risk

**NB**: Whilst many chemicals have been implicated in the development of lung cancer **passive smoking** is the most likely cause. Up to 15% of lung cancers in patients who do not smoke are thought to be caused by passive smoking.

<b><u>NB</u></b> : The most appropriate tool to confirm the diagnosis of bronchial carcinoma is >>> <b>Bronchoscopy ± Trans bronchial biopsy (NOT CT-guided FNA biopsy).</b>
--

## Non-small cell lung cancer (NSCLC)

There are **three** main subtypes of non-small cell lung cancer:

### 1) Squamous cell cancer:

- Typically central
- Associated with parathyroid hormone-related protein (PTHrP) secretion → hypercalcaemia.
- Hyperthyroidism due to ectopic TSH
- Strongly associated with finger clubbing.
- Hypertrophic pulmonary osteoarthropathy (HPOA)

**HPOA** is seen in patients with bronchial carcinoma.

It may **pre-date** the discovery of the underlying lesion.

It is characterised by **finger clubbing** and **long bone pain** (tender wrists without synovitis i.e. without stiffness, without limitation of movements).

The most sensitive diagnostic investigation is **isotope bone scan**: **increase** in the **uptake** in **long bones**, **around periarticular surfaces**, and also **mandible** and **scapulae**.

**X-Ray: Periosteitis over the ulna and radius.**

### 2) Adenocarcinoma:

- Most common type of lung cancer in non-smokers, although the majority of patients who develop lung adenocarcinoma are smokers.
- Typically located on the lung periphery.
- Normal bronchoscopy.
- Gynaecomastia.

**PET/CT scan** offers the best imaging modality to determine **LN** involvement in **bronchial adenocarcinoma**.

Lung adenocarcinoma:

- Most common type in non-smokers
- Peripheral lesion
- Normal bronchoscopy
- Gynecomastia

**NB: Bronchoalveolar cell carcinoma** classically presents with progressive breathlessness and the production of large amounts of sputum (**bronchorrhoea**). They account for up to 1% of all bronchial carcinomas.

The tumour spreads using the alveolar walls as a frame and the alveoli are often filled with mucin.

### **3) Large cell lung carcinoma:**

#### **Management of Non-small cell lung cancer:**

- Only 20% suitable for surgery.
- Prognosis after surgery is about 50-67% at 5 years with stage 1 disease
- Mediastinoscopy performed prior to surgery as CT does not always show mediastinal lymph node involvement.
- Curative or palliative **radiotherapy**.
- Poor response to chemotherapy.
- Survival advantages for **combined** radio and chemo therapy

#### **Surgery contraindications of Non-small cell lung cancer:**

- 1) Assess general health (age  $\geq$  70 yrs., IHD, **MI within 6 wks.**,  $\uparrow$  PCO<sub>2</sub>, etc.).
- 2) Stage IIIb or IV (i.e. **metastases** present).
- 3) **FEV1 < 1.5 litres** is considered a general cut-off point\*: as it means that there will be insufficient respiratory reserve post-surgery.
- 4) **MALIGNANT pleural effusion**
- 5) Tumour near hilum
- 6) Vocal cord paralysis (It implies extracapsular spread to mediastinal nodes and is an indication of inoperability).
- 7) SVC obstruction (SVCO)

\* However if FEV1 < 1.5 L for lobectomy or < 2.0 L for pneumonectomy then some authorities advocate further lung function tests as operations may still go ahead based on the results

Any Pt with malignancy or even disseminated malignancy and unknown primary, presents with oedema of the arms and face, persistent headache, with dilated neck veins >>> you suspect superior vena cava obstruction (SVCO).

Up to 4% of patients with lung cancer will develop SVCO at some point during their disease. Up to 10% of SCLC will present with SVCO.

**Both Non-small** cell cancer and **small** cell malignancy may cause SVCO.

SVCO is much more likely to be associated with **right sided lung lesion** 4 times than with left sided lesions.

**SVCO >>> It is an oncological emergency.**

CXR is abnormal in around 85% of cases, mediastinal widening is common.

Mediastinal radiotherapy leads to **symptomatic relief** in **80% of patients**, although case studies have shown this does not always correlate to patency of the superior vena cava.

Radiotherapy is useful but its effects are **not quick** enough.

If possible, an attempt should be made to obtain a **tissue diagnosis**, as some tumours respond to radiotherapy whereas others are more sensitive to chemotherapy.

Tumours which are very chemosensitive, such as germ cell and lymphoma, can cause SVCO.

**Dexamethasone IV** at **high** dose is of benefit in **severe** cases of SVCO + LMWH.

It is important to note that in 2004 NICE recommended considering **stenting** in the majority of cases of SVCO. This is a **minimally invasive** procedure which **relieves** symptoms **quicker than** chemotherapy or radiotherapy.

**SVCO >>> immediate management >>> Dexamethasone IV + LMWH.**

### **Small (oat) cell lung cancer (SCLC)**

Features:

- Usually central
- Arise from APUD\* cells
- Ectopic ADH → hyponatraemia

- Ectopic **ACTH** → ACTH secretion can cause bilateral adrenal hyperplasia, Cushing's syndrome (not typical, hypertension, hyperglycaemia, hypokalaemia, alkalosis, hirsutism and muscle weakness are more common than buffalo hump etc.)
- Lambert-Eaton syndrome: antibodies to voltage gated calcium channels (VGCC) causing myasthenic like syndrome.

**EX:** Male pt. chronic heavy smoker with chest infection plus hyperglycaemia + ↓ K + ↑ HCO<sub>3</sub> >>> should suspect **SCLC** with **ectopic ACTH secretion**.

**But** if with ↓Na and ↑K >>> think of **Adrenal metastasis** >>> **MRI adrenals**.

The following are adverse **prognostic factors** in **small cell lung cancer**:

- 1) Serum Na < 132 mmol/l
- 2) Weight loss > 10%
- 3) WHO performance status > 2
- 4) Alkaline phosphatase > 1.5 times upper limit of normal
- 5) LDH > 1.5 times upper limit of normal
- 6) Extensive disease (occurring outside one hemithorax and ipsilateral supraclavicular fossa nodes).

Management:

- **Usually metastatic disease by time of diagnosis**
- **Surgery**: it has **little** role, only used for debulking
- Most patients with limited disease now receive a **combination of chemotherapy and radiotherapy**
- Patients with more extensive disease are offered palliative **chemotherapy**.
- Prognosis for small cell cancer despite chemotherapy is little - 10% at 5 years.

**APUD**\* cells an acronym for:

- **Amine** - high amine content
- **Precursor Uptake** - high uptake of amine precursors
- **Decarboxylase** - high content of the enzyme decarboxylase

**Non-small NSCLC >>> Radiotherapy**

**Small SCLC >>> Chemotherapy**

Overall 5 year survival for lung cancer patients is still of the order of **14%**. (American Cancer Society 1998). i.e Overall lung cancer survival is less than 15% at five years.

This contrasts with approximately 50% for cancer of the breast and around 70% for cancer of the cervix.

### Bronchial Carcinoma

- 20-30% of cases with bronchial carcinoma are of small (oat) cell type from endocrine **K**- cells (**Kulchitsky**) cells.
- Primary bronchial cancer >>> the tumour edge may have **a fluffy or spiked appearance.**
- Paraneoplastic manifestations:
  - SIADH (5 - 10%)
  - ACTH (5 %)
  - ANP

### Stage grouping by TMN subset

		Tumour			
		T1	T2	T3	T4
Nodes	N0	IA	IB	IIB	IIIB
	N1	IIA	IIB	IIIA	IIIB
	N2	IIIA	IIIA	IIIA	IIIB
	N3	IIIB	IIIB	IIIB	IIIB

	Patient should be offered surgery if no medical contraindications and adequate lung function
	Surgery may be suitable for some patients, based on clinical judgement
	Not suitable for surgery

Stage IV = M1

**EX:** T3N1MX = stage III A



**Lung cancer: Paraneoplastic features**

Paraneoplastic syndromes are a result of antibody generation from or against malignant cells attacking normal tissue.

Both non-small cell and **small** cell lung cancers are associated with Paraneoplastic syndromes, although they are more common with the latter due to its neuroendocrine cell origin.

Examples include anti-neuronal antibodies (anti-Hu, anti-Yo, anti-Ri) directed against the Purkinje cells of the cerebellum leading to the **cerebellar syndrome** (ataxia).

The **Lambert-Eaton myasthenic syndrome (LEMS)** is a pre-synaptic disorder of auto-antibody IgG directed against the **pre-synaptic** voltage gated **calcium** channel (VGCC) leading to **impaired acetylcholine release**. Clinically, patients present with **proximal muscle weakness/ wasting** that **improves** with **exercise**.

Symptomatic hyponatraemia due to **SIADH** is treated with demeclocycline which induces nephrogenic diabetes insipidus leading to excretion of excess water.

**Lambert- Eaton syndrome** is characterised by:

- 1) Proximal muscle weakness (the cranial nerves and respiratory muscles are usually spared)
- 2) Depressed or absent tendon reflexes and
- 3) Autonomic features (for example, dry mouth, impotence, etc).

70% of cases are due to **small cell lung cancer**.

Unlike myasthenia gravis, **improved by exercise** which is associated with increasing muscle strength and there is a negative response to Tensilon.

**Electromyography** is useful in confirming the diagnosis where repeated nerve stimulations cause a progressive increase in the size of the muscle action potential.

**Eaton** (1905-1958) U.S. neurologist at Mayo Clinic. **Lambert** (1915-2003) U.S neuro-physiologist at Mayo Clinic and Prof. of physiology at University of Minnesota.

Paraneoplastic features of lung cancer:

- **Squamous cell**: PTHrp, TSH, Clubbing, HPOA
- **Adenocarcinoma**: Gynaecomastia
- **Small cell**: ADH, ACTH, Lambert-Eaton syndrome
- **Bronchial carcinoma**: SIADH, ACTH, ANP

**EX:** A 49-year-old man is diagnosed with **small cell lung cancer** + progressive truncal **ataxia** + **Normal brain MRI** >>>> **Paraneoplastic syndromes** >>> Diagnosis by: **Anti-Purkinje cell antibody levels**

**EX:** Male pt. 50 years old chronic heavy smoker with several episodes of haemoptysis, he is grossly oedematous, ascites, Hb=10, Creat=180, albumin=22. Urine protein +++, 5 gm proteinuria/day >>>? **Bronchial carcinoma** with **membranous GN** >> **BX: thickened glomerular BM** with **deposits of IgG and C3**.

### **Carcinoid Lung cancer:**

- The vast majority of bronchial adenomas are carcinoid tumours, arising from the amine precursor uptake and decarboxylation (APUD) system, like small cell tumours.
- Lung carcinoid accounts 1% of lung tumours and for 10% of carcinoid tumours.
- Classical carcinoid syndrome occurs in less than 10% of patients with carcinoid tumours, but occurs most commonly in those with tumours of the small intestine, appendix and proximal small bowel.
- Those in the lung rarely cause carcinoid, but have been associated with **ACTH secretion** and subsequent **Cushing's syndrome**.
- Other associated conditions where foregut carcinoid tumours are found in the pancreas are associated with Zollinger-Ellison syndrome and VIPoma.
- Carcinoid tumours are the most common neuroendocrine tumours, and usually originate in the **enterochromaffin** cells. The most common location is the **GIT**, but that can also occur in the bronchi and lungs.
- Carcinoid tumours of the lung (bronchial adenomas) (also called **argentafinomas** as they take up **silver**) are neuroendocrine cells and are **derived** from the **K cells (Kulchitsky) in the lung**.
- The masses are typically **silent**, but they can present due to **ectopic hormone** secretion or carcinoid heart disease.
- The carcinoid syndrome presents in approximately 10% of cases, more commonly those with GI tract primaries, and is predominantly due to release of 5-HT.
- The term bronchial adenoma is being phased out.

### **Lung carcinoid:**

- Typical age = 40-50 years
- The carcinoid syndrome characterised by **Skin flushing**, **bronchospasm**, **diarrhoea**, and **right-sided valvular heart lesions**.
- Smoking **NOT** risk factor

- Slow growing: e.g. **long history of cough, recurrent haemoptysis**
- Chest pain, breathlessness, wheeze and cough are less common.
- It accounts for between 1-5% of all lung tumours.
- Often centrally located and not seen on CXR
- It is usually occur in the major bronchi, 85% can be seen bronchoscopically.
- A carcinoid tumour in the left lower lobe bronchus could cause distal collapse of the left lower lobe.
- **'Cherry red ball'** is a typical finding that often seen on **bronchoscopy** (Bronchoscopy identifies up to 80% of carcinoid tumours in the main bronchi. It is a **highly vascular** 'cherry-like' tumour causing recurrent haemoptysis and bronchial obstruction. Biopsy is usually followed with brisk **bleeding** and should be done via **rigid** bronchoscopy).
- Carcinoid syndrome itself is rare (usually associated with **liver metastases**)
- **Plasma chromograffin A** is an effective **screening** test for carcinoid as it is very sensitive, but it is not specific.
- **24 hour urinary excretion of 5-hydroxyindoleacetic acid (5HIAA)** is more **specific** for the diagnosis, but false positives and negatives are present.

Management:

- Surgical resection: is the treatment of choice.
- But somatostatin analogues can be used where this is not possible.
- If no metastases then 90% survival at 5 years.

EX: A 38-year-old man presents with a 2 week history of recurrent haemoptysis which he has noted over the last 18 months. He is unaware of any chest pain and is a light smoker of five cigarettes daily. A CXR reveals collapse of the left lower lobe.

What is the most likely diagnosis? >>> **Bronchial carcinoid**

EX: A 40-year-old man is undergoing investigation for acromegaly. MRI of the pituitary fossa is normal, but a routine chest x ray reveals a large centrally based mass. The patient is a non-smoker.

What is the most likely type of this lung tumour >>> **Carcinoid Lung cancer**, which is secreting **GHRH** and resulting in **acromegaly**

**EX:** Young female + 4 month history of cough productive of mucoid sputum streaked with bright red blood + wheezing + diarrhoea >>>? **Carcinoid tumour >>> Bronchoscopy.**

The diagnosis of **phrenic nerve palsy** is suspected when on the CXR the **diaphragmatic leaflet is elevated** and is confirmed by **fluoroscopy** by observing **paradoxical diaphragmatic motion of the affected side** on sniff and cough.

In patients with normal lungs unilateral paralysis is usually asymptomatic and rarely requires treatment.

### **Lung cancer: referral**

The 2005 NICE cancer referral guidelines gave the following advice:

#### **Consider immediate referral for patients with:**

- Signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure).
- Stridor.

#### **Refer urgently patients with:**

- Persistent haemoptysis (in smokers or ex-smokers aged 40 years and older).
- A chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation).
- **A normal chest X-ray where there is a high suspicion of lung cancer.**
- A history of asbestos exposure and recent onset of chest pain, shortness of breath or unexplained systemic symptoms where a CXR indicates pleural effusion, pleural mass or any suspicious lung pathology.

#### **Refer urgently for chest x-ray for patients with any of the following:**

- Haemoptysis

- Unexplained or persistent (longer than 3 weeks): chest and/or shoulder pain, dyspnoea, weight loss, chest signs, hoarseness, finger clubbing, cervical or supraclavicular lymphadenopathy, cough, features suggestive of metastasis from a lung cancer (for example, secondaries in the brain, bone, liver, skin).
- Underlying chronic respiratory problems with unexplained changes in existing symptoms.

### Bronchiolitis Obliterans

- It is the term used to describe fibrous scarring of the small airway.
- Histologically there is a mural concentric narrowing of the lumina of the bronchioles.
- It can present as severe respiratory insufficiency.
- Inflammation in the small distal airways leads to **obstructive** spirometry and without treatment this is relentlessly progressive. **Air trapping** can occur, which leads to increased lung volumes.
- It is seen following: toxic fume inhalation, mineral dust exposure, viral infection (**CMV**), legionella, and mycoplasma, **bone marrow transplantation**, **heart lung transplantation**, **early acute rejection** and **CMV infection**, **Rheumatoid arthritis**, SLE, side effect of **penicillamine**.
- Dry cough, dyspnoea, wheezes
- CXR: vary from normal to a reticular or reticulonodular pattern.
- Diagnosis: confirmed by **lung biopsy**.
- Progressive and relentless **fall in (FEV<sub>1</sub>) the forced expiratory volume in one second** is the **most characteristic** of bronchiolitis obliterans.
- Prognosis is poor, Pts. rarely respond to **steroids**. Corticosteroids can induce a quick response and improvement in symptoms.

Bronchiolitis obliterans, with or without organising pneumonia, can be a **fatal** complication of **rheumatoid arthritis** (especially in **women** taking **penicillamine**).

Bronchiolitis obliterans has been seen as early as **3 months post-transplant**, like **heart** and **lung** or **BM** transplantation, and is responsible for **over 50% of deaths after the first year**.

**EX:** Pt underwent a heart-lung transplantation for pulmonary hypertension, then after 2 years develop SOB with obstructive pattern of PFTs >>>? **Bronchiolitis obliterans**

### **Azygous lobe**

An azygous lobe is seen in about **0.5%** of routine CXR

It is a **normal variant**. It has **little** clinical significance.

It is seen as a '**reverse comma sign**' behind the **medial end** of the **right clavicle** on the **upper zone** of the **right lung**.

It appears separated from the rest of the upper lobe by a deep groove (which contains the azygous vein). It develops in utero when the apical bronchus grows medial to the arch of the azygous vein instead of lateral.

### **Fat embolism**

The appearance of **multiple petechiae** in the distribution of the **axilla** or **upper body** is characteristic of a fat embolism.

The petechial rash is **pathognomonic** of this syndrome, but **only** occurs in **30-50%** of cases.

Unlike emboli that arise from a thrombus, fat emboli are **small** and **multiple** producing **widespread** effects. They may occur **1 to 3 days** following a **fracture** and are more common in **closed** fractures on the **long** bones or **pelvis** like femur.

The clinical features of fat emboli are predominately:

- 1) **Pulmonary** (shortness of breath, hypoxia)
- 2) **Neurological** (confusion and agitation)
- 3) **Dermatological** (petechiae) and
- 4) **Haematological** (thrombocytopenia, anaemia).

**EX:** A 31-year-old motorcyclist becomes **confused** and **dyspnoeic** on the orthopaedic ward 24 hours after fracturing his right **femur** in an accident.

Which of the following **skin** lesions may be found on examination? Fat embolism  
>>> Multiple petechiae in both axilla.

## Chronic cough

In epidemiological studies 16% of the UK population reported a persistent cough.

For the purposes of the BTS guidelines, cough is a forced expulsive manoeuvre against a closed glottis with a characteristic sound.

**Acute cough** is defined as one lasting **less than 3 weeks**.

**Chronic cough** is defined as one lasting **over 8 weeks**

(كحة مزمنة لأكثر من شهرين)

There is a **grey area** between 3 to 8 weeks and this includes **post-viral coughs**.

## WHO scale for Performance Status

Assessing a patient's performance status is important when evaluating the most appropriate treatment options.

It is commonly used by **cancer** MDTs, but has a role in assessing patients with **chronic illnesses** including **COPD**.

WHO (Zubrod) Scale	Description
0	Asymptomatic
1	Symptomatic but <b>ambulatory</b> (can carry out light work)
2	In bed <b>less than 50%</b> of the day. Unable to work but can live at home with some assistance
3	In bed <b>more than 50%</b> of the day (unable to care for self)
4	Bedridden

### **Smoking in pregnancy**

Smoking **reduces birth weight** which may be of critical importance if the baby is born pre-term.

On average, the babies of smokers weigh 170 g less than non-smokers, but the **reduction in birth weight is related to the number of cigarettes smoked per day**.

Smoking is also associated with an increased risk of **miscarriage** and **still birth**. The infant has a greater risk of **sudden infant death syndrome**.

There is some evidence that maternal smoking may adversely **affect ovarian function in female children**.

**No dysmorphic facies** syndrome has yet been described.

Maternal smoking has been shown to **increase lung maturity** ☺ , possibly by enhancing the production or secretion of cortisol. This makes neonates less likely to develop respiratory distress syndrome☺, but as lung maturation is often abnormal babies may have reduced lung function and increased rates of other respiratory illnesses.

### **Pulmonary Alveolar Proteinosis (PAP)**

It is a rare diffuse lung disease in which the alveolar sacs become filled with protein-rich fluid that characteristically stain for **PAS**, a protein derived from surfactant.

It usually affects people aged between **20-60 years** who have **no previous** lung disease, **men** more frequently than women.

It can be primarily or secondary, the latter being related to infections with, for example, pneumocystitis Jirovecii or atypical mycobacteria, or to immunosuppressants, organic dusts and haematological malignancy.

It usually presents with **SOB** and **mild constitutional symptoms**.

Diagnosis based on **bronchial lavage** or **biopsy** with **PAS-positive stains** and increased presence of **surfactant proteins A and D**.

**HRCT** chest shows a classical picture of **dense infiltrates**, often referred to as **crazy paving**.

**Spirometry** shows a **restrictive pattern** with reduced lung capacity and reduced CO diffusion.

Most patients do not require ttt unless their SOB is disabling.



TTT is by **washing the alveoli out** with salt solution. This can be done with bronchoscopy or under general anaesthesia through the trachea. If both lungs need washing then they are done about 5 days apart. The number of washing depends on symptoms.

Prognosis is **good**.

### **Ludwig's angina**

It is rapidly spreading, life threatening cellulitis of the **sublingual** and **submandibular** spaces that usually starts in an infected lower mole.

Airway obstruction and difficulty in breathing and talk may result as the infection spreads to the supraglottic tissues.

TTT: IV antibiotic against streptococci and oral anaerobes and **take care of airway (call anaesthesiologist)**.

### **Alveolar microlithiasis**

It is a rare condition, sometimes familial with **autosomal recessive** inheritance, with **female** predominance 2:1.

It is associated with deposition of **diffuse calcified microliths in alveolar space**.

Unfortunately progressive Ca deposition leads to **respiratory failure** with early age death.

CXR or CT: **fine micronodular calcification** predominantly at lung **base** and **hila**.

PFT shows **restrictive** pattern.

No medical intervention has proved successful, although lung transplantation has been used for some cases.

So much Ca deposition, the examined lungs at post-mortem were as so stiff as to require a saw to enable sectioning for examination.

### **Post-extubation stridor (PES)**

PES is a **frequent** complication of intubation, occurring in **2-16%** of cases.

It is caused by laryngeal oedema that results from damage to the mucosa of the larynx.

Mucosal damage is caused by pressure and ischaemia resulting in an inflammatory response.

Laryngeal oedema, in severe cases, can lead to acute respiratory compromise necessitating emergency re-intubation.

Risk factors for PES include:

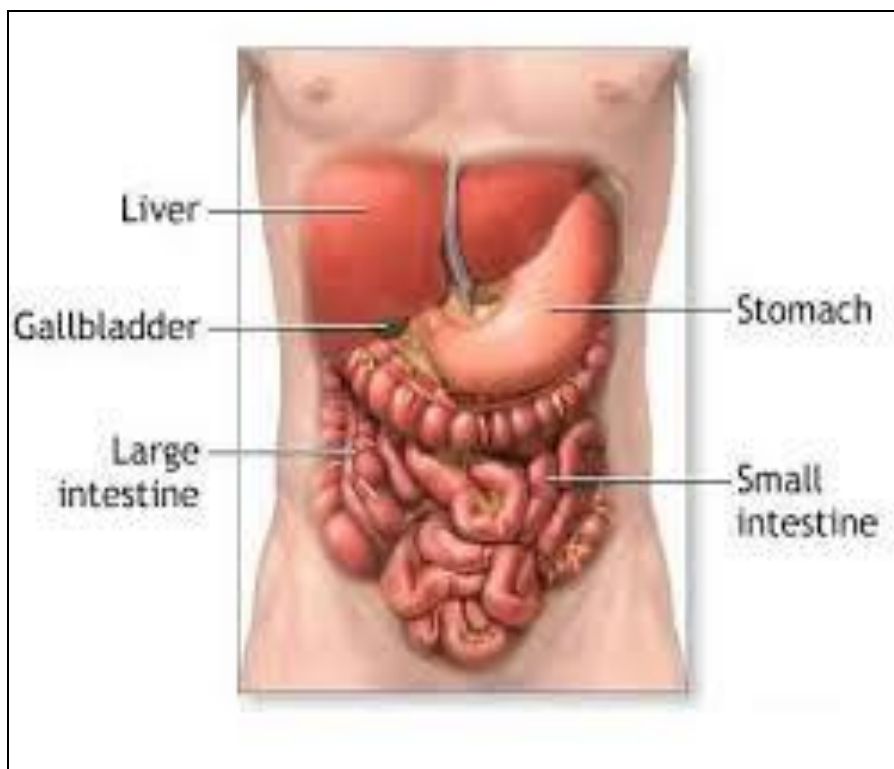
- 1) **Female** gender: may be due to the female mucous membrane being less resistant to trauma and thinner than that in men.
- 2) Intubation **>36 hours**.
- 3) **Excessive** cuff pressure.
- 4) **Large** tube size.
- 5) Tracheal **infection**.

NB: Age and asthma are not known risk factors for PES.

### **Lymphangiomyomatosis**

See link

# Gastroenterology & Hepatology



Gastrointestinal hormones

Below is a brief summary of the major hormones involved in food digestion:

	Source	Stimulus	Actions
<b>Gastrin</b>	<b>G</b> cells in <b>antrum</b> of the stomach	<b>Distension</b> of stomach, swallowing, Vagus nerves (mediated by gastrin-releasing peptide), luminal peptides/amino acids. Ach, histamine  <b><u>Inhibited by:</u></b> Low antral pH, Somatostatin. Prostaglandin	<b>Increase HCL</b> , pepsinogen and IF secretion, <b>increases gastric motility</b> , stimulates parietal cell maturation
<b>CCK</b>	<b>I</b> cells in <b>upper small intestine</b>	Partially digested proteins and triglycerides	<b>Stimulates contraction of the gallbladder.</b> Increases secretion of enzyme-rich fluid from pancreas, contraction of gallbladder and relaxation of sphincter of Oddi, decreases gastric emptying, trophic effect on pancreatic acinar cells, induces satiety
<b>Secretin</b>	<b>S</b> cells in upper small intestine	Acidic chyme, fatty acids	<b>Increases</b> secretion of <b>HCO<sub>3</sub><sup>-</sup></b> -rich fluid from <b>pancreas</b> and <b>liver</b> . <b>Decreases gastric</b> acid secretion. Trophic effect on pancreatic acinar cells.
<b>VIP</b>	Small intestine, pancreas	Neural	It is a <b>vasodilator</b> and also regulates <b>smooth muscle activity, epithelial cell</b>

	Source	Stimulus	Actions
			<b>secretion and gastrointestinal blood flow.</b> Stimulates secretion by pancreas and intestines, inhibits acid secretion
<b>Somatostatin</b>	D cells in the <b>pancreas &amp; stomach</b>	Fat, bile salts and glucose in the intestinal lumen	<b>Inhibits all gastrointestinal endocrine secretions:</b> Decreases acid and pepsin secretion, decreases gastrin secretion, decreases pancreatic enzyme secretion, decreases insulin and glucagon secretion inhibits trophic effects of gastrin, stimulates gastric mucous production

#### Pancreatic cells:

- Islet **A** cells produce **glucagon**
- Islet **β** cells produce: **insulin** and **amylin**, as well as **C peptide**, **pro-insulin** and **GABA**.
- Islet **D** cells produce **somatostatin**
- Islet **F** cells produce **pancreatic polypeptide**

Gastric **chief** cells produce: **pepsinogen**

Gastric **parietal** cells produce **HCL** and **intrinsic factor (IF)**.

#### VIPoma

VIPoma is a vasoactive intestinal polypeptide (VIP) secreting tumour occurring mainly in the **pancreas**.

It is a gut neuroendocrine tumour

It is rarely a ganglioneuroblastoma (sympathetic chain or adrenal cortex).

The normal functions of VIP are:

- Peripheral vasodilation

- Increased intestinal secretion of water and electrolytes
- Inhibition of gastric acid secretion, and
- Potentiates acetylcholine action on salivary glands.

VIPomas are endocrine tumours that secrete excessive amounts of VIP 32 which cause a distinct syndrome characterised by:

- 1) **Large-volume watery diarrhoea** (usually **more than 700 mL/day**)
- 2) **Dehydration.**
- 3) **Hypokalaemia**
- 4) **Acidosis** (due to loss of alkaline secretions)
- 5) **Achlorhydria:** High gastric PH
- 6) **Hyperglycaemia**
- 7) **Serum Chromogranin A** is **elevated** in the majority of neuroendocrine tumours with the exception of Insulinoma.

This syndrome is also called **Verner-Morrison syndrome, pancreatic cholera, or WDHA syndrome** for: **W**atery **D**iarrhoea, **H**ypokalaemia, and **A**chlorhydria, which some patients develop.

It can occur in children and when it does is usually caused by a ganglioneuroma or ganglioneuroblastoma.

TTT:

- **Medical** management of choice is with **somatostatin analogues**, often small doses lead to a cessation of symptoms.
- **Codeine** prolongs small bowel transit time and increases stool water absorption, it may be an adjunct in patients who do not adequately respond to somatostatin.
- Non-metastatic tumours can be surgically resected.

A stool volume of <700 mL/d excludes the diagnosis of VIPoma.

**Achlorhydria** is classically associated with VIPoma together with **profuse diarrhoea**, a **hypokalaemic acidosis** and **hyperglycaemia**.

Although raised pancreatic polypeptide is seen with a VIPoma it is unusual and is more commonly associated with its own syndrome.

**NB:** Migratory erythema is associated with a Glucagonoma.

**NB:** Pellagra is associated with the carcinoid syndrome.

## GORD

### Overview:

- Poor correlation between symptoms and endoscopy appearance.
- It occurs during transient relaxation of the lower oesophageal sphincter (LES).

### Indications for upper GI endoscopy:

- Age > 55 years
- Symptoms > 4 weeks or persistent symptoms despite treatment
- Dysphagia
- Relapsing symptoms
- Weight loss

If endoscopy is negative >>> consider **24-hr oesophageal pH monitoring** (the **gold** standard test for diagnosis of GERD).

24hr oesophageal pH monitoring >>> is gold standard investigation in GORD

Monitoring of pH is not a good guide to therapy but symptomatic improvement is a good guide to the efficacy of therapy.

**Laparoscopic fundoplication** is the treatment of choice for patients with GORD **refractory** to or intolerant of proton pump inhibitor therapy.

The patient should have had an **endoscopy within the 6 months prior** to surgery to exclude any unsuspected pathology such as Barrett's oesophagus or adenocarcinoma.

An **oesophageal transit study** is indicated to rule out a primary motor disorder (for example, achalasia, scleroderma) when suspected and to rule out aperistalsis, which may result in postoperative dysphagia after some forms of fundoplication.

Pt with severe GERD, so the most useful test in assessing the role of surgery is >>> **Oesophageal motility and pH study**

## Barrett's oesophagus

Barrett's refers to the metaplasia of the lower oesophageal mucosa, with the usual squamous epithelium being replaced by columnar epithelium.

It is associated with GERD in 10% of patients.

It is a **pre-malignant** condition and can result in an increased risk of oesophageal **adenocarcinoma**, estimated at **50-100 folds**.

The risks of adenocarcinoma are relatively high (30 × normal) but absolute risk is low 1% per year develop adenocarcinoma.

Histological features: The columnar epithelium may resemble that of either the cardiac region of the stomach or that of the small intestine (e.g. with goblet cells, paneth cells, brush border).

Management:

- The **first** line ttt is **High dose PPIs for 8-12 weeks and then re-endoscopy** in low grade dysplasia.
- If some improvement is seen, then **6 monthly review** is suggested until stable/improved disease has been identified on at least 2 successive endoscopies.
- Once this milestone has occurred, surveillance can be reduced **to 2 yearly**.
- Endoscopic surveillance with biopsies **every 2 years** in general, but annually in high-risk patients.
- **Cryotherapy**: it offers the most promising results, complete reversal in 78% of patients 6 months after ttt.
- **Oesophagectomy**.

**BSG: Barrett's oesophagus with NO / low grade dysplasia>>> High dose PPIs for 8-12 weeks and then re-endoscopy and biopsy in 2 years.**

### Oesophageal cancer

Until recent times oesophageal cancer was most commonly due to a squamous cell carcinoma which found mainly in the upper and middle third of the oesophagus but the incidence of **adenocarcinoma** is rising rapidly.

**Adenocarcinoma** is now the most common type of oesophageal cancer and is more likely to develop in patients with a history of gastro-oesophageal reflux disease (GORD) or Barrett's. The majority of this tumours are in the lower third of the oesophagus.

Risk factors:

- Smoking
- Alcohol
- GORD
- Barrett's oesophagus
- Achalasia
- Plummer-Vinson syndrome
- Rare: coeliac disease, scleroderma



## Achalasia

- Failure of oesophageal peristalsis and of relaxation of lower oesophageal sphincter (LOS) due to degenerative loss of ganglia from Auerbach's plexus i.e. LOS contracted, oesophagus above dilated.
- Achalasia can present at any age but typically presents in middle-age most often in the 3<sup>rd</sup> to 5<sup>th</sup> decades.
- It is equally common in men and women.
- It affects an estimated 10 in 10,000 people.

### Clinical features:

- Symptoms usually develop **years** before the patient presents
- Typically variation in severity of symptoms
- Dysphagia of BOTH liquids and solids
- Heartburn
- **Vague chest discomfort** is common
- Regurgitation of food - may lead to cough, aspiration pneumonia (30% have a **nocturnal cough** due to aspiration of oesophageal contents).
- Malignant change in small number of patients

A longstanding history of dysphagia to both solids and liquids suggests a functional rather than mechanical cause for the dysphagia.

### Investigations:

- 1) **Oesophageal manometry**: excessive LOS tone which doesn't relax on swallowing - considered most important definitive diagnostic test.
- 2) **Barium swallow** shows grossly expanded oesophagus, typical bird's peak appearance, fluid level.
- 3) **CXR**: not specific, wide mediastinum, fluid level.

The gold standard test for **achalasia** is >>>> **oesophageal manometry**

### Treatment:

- 1) **Heller cardiomyotomy**: good to excellent symptom response in 82% of patients and show symptom response rates of 84-100%.
- 2) Balloon dilation: is usually attempted before laparoscopic surgical myotomy.
- 3) Intra-sphincteric injection of botulinum toxin: its effects are short lived (typically < 6 months) and use is generally recommended to be restricted to the frail or elderly in whom more aggressive therapy poses high risk.
- 4) Drug therapy like nifedipine and nitrates has a role but is limited by side-effects.

### Pharyngeal pouch (Oesophageal diverticulae)

A pharyngeal pouch is a posteromedial diverticulum through Killian's dehiscence. Killian's dehiscence is a triangular area in the wall of the pharynx between the thyropharyngeus and cricopharyngeus muscles. It is more common in older patients and is 5 times more common in men.

#### Features:

- Dysphagia to solids and liquids
- Regurgitation of rotten undigested food
- Halitosis
- Nocturnal chronic cough
- Aspiration >> pneumonia
- Neck swelling which gurgles on palpation

**Diagnosis: Barium swallow.**

**Management: Surgical**

- Either diverticulectomy for larger lesions, or
- Dohlman's procedure for smaller pouches.

### Esophageal Rupture and Tears

**Mackler's triad (vomiting, chest pain and surgical emphysema)** is classical but absent in almost half the cases.

EX: Severe sudden onset chest pain during a paroxysm of vomiting and pleural effusion >>> raise the suspicion of oesophageal rupture.

The chest x ray may confirm the surgical emphysema.

A **gastrograffin swallow** is **diagnostic** and identifies the site and extent of rupture. This may determine the most appropriate treatment. However, it has a false negative rate of at least 10%.

A **CT scan** should be done if a gastrograffin swallow is not possible or negative. as of oedema and haemorrhage a CT scan **may not** identify the site of the perforation.

**Lateral neck x rays** may be useful in the **early** stages where the diagnosis is uncertain and surgical emphysema is **not** seen on a plain CXR.

**Oesophagoscopy** has a role in **if** the gastrograffin swallow is negative.

**Esophageal Rupture >>> Gastrograffin swallow** is diagnostic

### Boerhaave's syndrome

**Repeated vomiting** followed by **severe epigastric pain** and **pleural effusion** with somewhat **respiratory distress** >>> **spontaneous oesophageal rupture** (Boerhaave's syndrome).

It is relatively uncommon but **serious** and **potentially fatal**.

It is complete **transmural laceration** of the lower part of the oesophagus with gastric contents entering the mediastinum and pleural cavity.

It is more common in **men** than women and typically present in those between **50-70 years old**.

**Early operation** after **appropriate resuscitation** offers the best chance of survival.

### Oesophageal varices

#### Acute treatment of variceal haemorrhage:

- ABC: patients should ideally be resuscitated prior to endoscopy
- Correct clotting: FFP, vitamin K
- Vasoactive agents: terlipressin is currently the only licensed vasoactive agent and is supported by NICE guidelines. It has been shown to be of benefit in initial haemostasis and preventing rebleeding. Octreotide may also be used although there is some evidence that terlipressin has a greater effect on reducing mortality.
- Prophylactic antibiotics have been shown in multiple meta-analyses to reduce mortality in patients with liver cirrhosis.
- Endoscopy: endoscopic variceal band ligation is superior to endoscopic sclerotherapy. NICE recommend band ligation.
- Sengstaken-Blakemore tube if uncontrolled haemorrhage.
- Transjugular Intrahepatic Portosystemic Shunt (TIPSS) if above measures fail.

Antibiotic prophylaxis reduces mortality in cirrhotic patients with GIT bleeding

**Terlipressin** - method of action >>> constriction of the splanchnic vessels

#### Prophylaxis of variceal haemorrhage:

- Propranolol: reduced rebleeding and mortality compared to placebo.

- Endoscopic variceal band ligation (EVL) is superior to endoscopic sclerotherapy. It should be performed at two-weekly intervals until all varices have been eradicated.
- Proton pump inhibitor cover is given to prevent EVL-induced ulceration.

**N.B:**

- Endoscopic sclerotherapy now has little role in the prophylaxis of variceal haemorrhage.
- Propranolol is used in the primary prophylaxis of variceal haemorrhage.
- Terlipressin is used in the management of acute variceal haemorrhage.
- Terlipressin is the only licensed vasoactive agent for variceal haemorrhage in the UK.
- Terlipressin dose is 2 mg IV stat followed by 1- 2 mg every four to six hours for 72 hours or until the bleeding stops. It is contraindicated in patients with known vascular disease or an ischaemic ECG.

**Hematemesis**

There are a number of available scoring systems which stratify subjects with gastrointestinal bleed into high and low risk groups.

**The Rockall scoring system** is based on:

- 1) **Age** (the higher the age the worse the prognosis)
- 2) Comorbidities, e.g. ischaemic heart disease (**IHD**)
- 3) Presence of shock
- 4) Endoscopic abnormalities: (diagnosis & evidence of bleeding).

	Score 0	Score 1	Score 2	Score 3
<b>Age</b>	<60	60-79	>80	-
<b>Shock</b>	No shock	Pulse >100	SBP <100 mmHg	-
<b>Co-morbidity</b>	Nil major		CCF, <b>IHD</b> , major morbidity	<b>Renal</b> or <b>liver</b> failure, <b>metastatic</b> cancer
<b>Diagnosis</b>	Mallory-Weiss tear	All other diagnoses	GI malignancy	-
<b>Evidence of bleeding</b>	None	-	Blood, adherent clot, spurting vessel	-

Increasing scores are strongly correlated with increasing risk of mortality, correlation with risk of re-bleeding is also present but not as strong.

Each category is scored between 0 and 2 points, with the exception of co-morbidities which has a maximum score of 3.

The weighting of points corresponds to the additional risk of death that parameter confers.

**Renal failure, liver failure and metastatic cancer** carry the **highest** points, and thus confer the highest risk of death, of any of the other parameters included in the scoring system.

An endoscopic finding of gastric ulcer confers a single point.

The **Hb level is not included** within the Rockall scoring system. It is included within an alternative scoring system known as the Blatchford score.

**The Canadian Consensus Conference Statement** utilises a similar system, incorporating endoscopic factors including:

- Active bleeding
- Major stigmata of recent haemorrhage
- Ulcers greater than 2 cm in diameter
- The location of ulcers in proximity to large arteries.

**The Baylor bleeding score** attaches a score to pre- and post-endoscopic features.

**The Blatchford score** is based on clinical parameters alone:

- Elevated **BUN**
- Reduced **haemoglobin**
- A drop in **systolic blood pressure**
- Raised **pulse rate**
- The presence of melaena or syncope
- Evidence of hepatic or cardiac disease.

In severe hematemesis with the presence of large bleeding duodenal ulcer and unable to reach it by scope >>> **Angiography with selective embolisation.**

The right and left gastroepiploic arteries supply the **greater** curvature of the stomach.

The right gastric artery is mainly found to supply the pylorus and the **lesser** curvature of the stomach.

**EX:** Pt with recurrent attacks of melena and now he is free, OGD and colonoscopy both are unremarkable >>> So, **Meckel's Scan** or **capsule enteroscopy**.

Hematemesis due to **oesophageal varices** >>> **Terlipressin**.

Hematemesis due to **bleeding PU** >>> **IV omeprazole**, it has been proven in a number of meta-analyses to impact positively on mortality when used in addition to optimal endoscopic injection therapy.

### Meckel's diverticulum

Meckel's diverticulum is the vestigial remnant of the omphalomesenteric duct.

It is normally located in **the terminal ileum within ~60 cm of the ileocaecal valve** and it averages **6 cm in length**.

About **50%** of these contain **ectopic gastric mucosa**, commonly leading to clinical presentations of peptic ulceration and haemorrhage.

Other complications of Meckel's diverticulum include

- Diverticulitis
- Intussusception
- Perforation
- Obstruction.

Although it occurs much more commonly in **children** it is an important differential consideration for gastrointestinal bleed in adults.

**Tc-99m pertechnetate** accumulates in gastric mucosa and is the study of choice for identifying ectopic gastric mucosa in a Meckel's diverticulum.

**EX:** A 14-year-old boy presents with a 2 day history of right lower quadrant abdominal pain and passage of bright red blood per rectum.

O/E there is tender in the right iliac fossa and bright red blood was found on rectal examination >>>? **Meckel's diverticulum** >>> pre-operatively diagnosis is by **Tc-99m pertechnetate**.

### **Helicobacter pylori (H-Pylori)**

Helicobacter pylori is a Gram negative bacteria associated with a variety of gastrointestinal problems, principally peptic ulcer disease.

#### **Associations:**

- 1) Peptic ulcer disease (PUD): (95% of **duodenal** ulcers (DU), 75% of gastric ulcers (GU)).
- 2) Gastric cancer.
- 3) B cell lymphoma of MALT tissue (treatment by eradication of H pylori results causes regression in 80% of patients).
- 4) Atrophic gastritis.

**N.B:** The role of H pylori in Gastro-oesophageal reflux disease (GORD) is unclear - there is currently no role in GORD for the eradication of H pylori.

#### **Management:**

Eradication may be achieved with a **7 day** course of **triple therapy**:

- A proton pump inhibitor + amoxicillin + clarithromycin, or
- A proton pump inhibitor + metronidazole + clarithromycin

Triple therapy is **for 1 week** as studies now show that 2 weeks of treatment is no more effective than 1 week.

**Two weeks** of therapy is considered when a **MALT lymphoma** has been identified.

#### **Sequential triple therapy for 10 days:**

- First 5 days: PPI + Amoxicillin
- Second 5 days: PPI + Clarithromycin + Tinidazole (Fasigyn®)

**EX:** A man developed **Helicobacter pylori** related duodenal ulcer after **kidney transplantation**. The most reasonable eradication treatment regimen is (**Pantoprazole + Metronidazole + Tetracycline + Bismuth**)

Quadruple therapy containing a PPI, bismuth, metronidazole, and tetracycline, has been shown in meta-analysis of comparative RCTs to achieve a **similar eradication rate** to **clarithromycin-based triple therapy**.

**Clarithromycin** interacts with cyclosporine. Being an **enzyme inhibitor**, this macrolide will result in an (**undesirable**) **increase** the blood level of **cyclosporine**.

**Urea breath test –**

No antibiotics in past 4 wks, no antisecretory drugs (e.g. PPI) in past 2 wks.

**Gastric MALToma (Gastric Mucosa Associated Lymphoid tissue)** is characterized by large numbers of immunocompetent cells in the lamina propria. MALTomas are B-cell lymphomas comprising **large numbers of lymphocytes with irregular nuclear contours and abundant cytoplasm.**

Higher-grade lymphomas show clusters or sheets of blast-like cells.

Up to **75%** of **small low-grade lymphomas** may regress **completely** after antibiotic therapy for **H-pylori eradication.**

Where treatment fails, surgical therapy or combinations with radio- and chemotherapy may be considered.

In addition, **Imatinib mesilate (Glivec)** has recently shown a good deal of success in achieving remission in this condition.

**NB:** Patients with gastric ulceration tend to suffer from anorexia and weight loss while those with a **duodenal ulcer maintain or gain weight.**

The characteristic clinical feature which aids the diagnosis is abdominal pain which is **relieved by eating.**

**Helicobacter pylori: tests**

**Urea breath test (UBT):**

- Patients consume a drink containing carbon isotope 13 (<sup>13</sup>C) enriched urea
- Urea is broken down by *H. pylori* urease
- After 30 mins patient exhale into a glass tube
- Mass spectrometry analysis calculates the amount of <sup>13</sup>C CO<sub>2</sub>
- Should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of an antisecretory drug (e.g. a PPI).
- **Sensitivity 95-98%, specificity 97-98%**
- Re-testing for *Helicobacter pylori* is indicated only in the setting of PUD to confirm eradication where an initial test is positive.

**Rapid urease test (e.g. CLO test):**

- Biopsy sample is mixed with urea and pH indicator
- Colour change if *H. pylori* urease activity
- Sensitivity 90-95%, specificity 95-98%



**Serum antibody:**

- Remains positive after eradication
- Sensitivity 85%, specificity 80%

**Gastric biopsy**

- Histological evaluation alone, no culture
- Sensitivity 95-99%, specificity 95-99%

**Culture of gastric biopsy**

- Provide information on antibiotic sensitivity
- Sensitivity 70%, specificity 100%

**Stool antigen test**

- Sensitivity 90%, specificity 95%.
- Whilst stool antigen testing is appropriate in the setting of initial diagnosis the NICE guidelines on dyspepsia do not recommend its use to confirm eradication due to a lack of evidence.

<p><b><u>N.B</u></b> The <b>urea breath test (UBT)</b> is highly sensitive, specific and non-invasive. There is no indication for an endoscopy. <b>Stool antigen</b>, rather than culture, is an alternative.</p>
---

**Dyspepsia**

In 2004 NICE published guidelines for the management of dyspepsia in primary care. These take into account the age of the patient (whether younger or older than 55 years) and the presence or absence of '**alarm signs**':

- 1) Chronic gastrointestinal bleeding
- 2) Progressive unintentional weight loss
- 3) Progressive difficulty swallowing
- 4) Persistent vomiting
- 5) Dysphagia
- 6) Iron deficiency anaemia
- 7) Epigastric mass
- 8) Suspicious barium meal

### Deciding whether urgent referral for endoscopy is needed:

Urgent referral (within 2 weeks) is indicated for patients with any alarm signs irrespective of age.

Routine endoscopic investigation of patients of any age, presenting with dyspepsia and without alarm signs is not necessary, however Patients aged 55 years and over should be referred urgently for endoscopy if **dyspepsia** symptoms are:

- Recent in onset rather than recurrent and
- Unexplained (e.g. New symptoms which cannot be explained by precipitants such as NSAIDs) and
- Persistent: continuing beyond a period that would normally be associated with self-limiting problems (e.g. Up to four to six weeks, depending on the severity of signs and symptoms)

### Criteria for referral for urgent endoscopy include:

- Dysphagia (at any age).
- Dyspepsia at any age combined with any one of weight loss, anaemia or vomiting.
- Dyspepsia in a patient aged 55 or above with onset of dyspepsia within one year and persistent symptoms.
- Dyspepsia with one of Barrett's oesophagus, family history of upper gastrointestinal (GI) carcinoma, pernicious anaemia or upper GI surgery more than 20 years ago.
- Jaundice.
- Abdominal mass.

### Managing patients who do not meet referral criteria ('undiagnosed dyspepsia')

This can be summarised at a step-wise approach:

- 1. Review medications for possible causes of dyspepsia
- 2. Lifestyle advice
- 3. Trial of full-dose PPI for one month\*
- 4. 'Test and treat' using carbon-13 urea breath test

\*it is unclear from studies whether a trial of a PPI or a 'test and treat' should be used first.

**NICE** guidelines state in **middle** age group with **dyspepsia**, in the **absence** of **alarm** symptoms, should be **treated with lifestyle advice and PPI** if needed. If after **one month** symptoms are not controlled then **testing for H-pylori** (UBT) could be

carried out. There need to be a **2 weeks wash-out period** off the PPI for breath test to be reliable.

So, young person with dyspepsia with no alarm signs >>> **prescribe a PPI** and **review symptoms in one month**.

### **Zollinger-Ellison syndrome (ZES)**

Zollinger-Ellison syndrome is a rare condition characterised by excessive levels of gastrin, usually from a **gastrin** secreting tumour usually of the duodenum or pancreas.

Gastrin is mainly produced in two forms by the **G cells** of the **gastric antrum**.

It stimulates the parietal cells to produce HCL and its production is **stimulated** by neural reflex pathways and also by the **direct effect of digested gastric luminal peptides** on the G cells themselves.

Gastrin may have some effect in stimulating exocrine pancreatic secretions.

ZES is under-diagnosed and it is **malignant** in approximately **60%** of cases.

5 year survival rate of 80% for a single tumour.

Around 30% occur as part of **MEN type I** syndrome.

#### **Features:**

- 1) **Multiple gastroduodenal ulcers.**
- 2) **Diarrhoea:** may be the only presenting symptom.
- 3) **Malabsorption:** Vit B12 deficiency >> Macrocytic anaemia.

Zollinger-Ellison syndrome (ZES) >> Epigastric pain and diarrhoea

#### **Diagnosis:**

- 1) **Fasting gastrin levels on 3 different days:**
  - The single best screen test.
  - Patient should stop PPI for at least 1 week before the test to avoid false positive results,
  - It should be done for 3 separate days as the secretion of gastrin is pulsatile,
  - Three samples in the normal range make a gastrinoma unlikely.
- 2) Secretin stimulation test: leads to marked elevation in gastrin levels, used if there is doubt as to the diagnosis with only a mild elevation of serum gastrin.
- 3) Radioisotope scan: hot spots of tumour expressing somatostatin receptors.

CT abdomen has a sensitivity of only 50% for primary tumours in ZES. Normal levels of fasting gastrin in untreated ZES are extremely rare.

Other causes of **elevated serum gastrin** is **atrophic gastritis** and **PPI** ttt.

### TTT:

- High-dose PPIs are needed to control the symptoms
- Octreotide: to reduce gastrin secretion.
- Surgical resection of the gastrin adenoma.

### MEN-I:

- **Parathyroid** (95%): hyperparathyroidism due to parathyroid hyperplasia
- **Pituitary** (70%): prolactinoma
- **Pancreas** (50%, e.g. Insulinoma, gastrinoma)

Serum **fasting gastrin** levels **above 1,000** (Normal < 200 pg/ ml) with **low gastric pH < 2** are strongly indicative of a **gastrinoma** >>> the patient should be subject to **Secretin stimulation test**.

Secretin is the first choice, and a rise of greater than 200 15 minutes after dosing is a pointer towards a gastrinoma as the underlying diagnosis. **It would be sensible to perform the secretin first, prior to attempting pancreatic imaging.**

He should not be committed to high dose PPI therapy until gastrinoma has been ruled out.

## Gastric cancer

### Epidemiology:

- The incidence of distal stomach tumours is actually decreasing while the incidence of **tumours in the proximal stomach (the cardia)** is increasing.
- Peak age = 70-80 years.
- More common in Japan, China, Finland and Colombia than the West.
- More common in males, 2:1

### Associations:

- Chronic H. pylori infection
- Blood group **A**: g**A**strik c**A**ncer
- Gastric adenomatous polyps
- Pernicious anaemia
- Smoking

- Alcohol
- Diet: salty, spicy, **nitrates (nitrosamines)** and **smoked** foods.
- Occupational exposure to heavy metals, rubbers, asbestos.
- May be negatively associated with duodenal ulcer

**NSAID** use is associated with **decreased** risk of certain gastric tumours ☺

### Investigation:

- Diagnosis: endoscopy with biopsy
- Staging: CT or endoscopic ultrasound - **endoscopic ultrasound (EUS) has recently been shown to be superior to conventional CT** as it is able to assess depth of infiltration and lymphatic dissemination of tumour.
- Screening for gastric carcinoma in Japan detects up to 40% of gastric carcinomas at an early stage and in skilled hands **5 year survival** can be upwards of **90%**.

### **Non-alcoholic fatty liver disease**

Non-alcoholic fatty liver disease (NAFLD) is now the most common cause of liver disease in the developed world. It is largely caused by obesity and describes a spectrum of disease ranging from:

- Steatosis - fat in the liver.
- Steatohepatitis - fat with inflammation, non-alcoholic steatohepatitis (**NASH**), see below.
- Progressive disease may cause fibrosis and liver cirrhosis.

NAFLD is thought to represent the hepatic manifestation of the **metabolic syndrome** and hence **insulin resistance** is thought to be the key mechanism leading to steatosis.

Non-alcoholic steatohepatitis (**NASH**) is a term used to describe **liver Biopsy histopathological changes similar** to those **seen in alcoholic hepatitis** in the **absence** of a history of **alcohol abuse** or consume **less** than 40 g of alcohol / week.

NASH is a **silent** liver disease and it is **almost always asymptomatic** and diagnosed **incidentally**.

The diagnosis is supported by the presence of **obesity**, **hyperglycaemia**, **hyper echogenic** hepatic parenchyma and **↑ ALT > AST**

It is relatively common and thought to affect around **3-4%** of the general population. It is more common in **men** due to the protective effects of oestrogen.

The progression of disease in patients with NASH may be responsible for a proportion of patients previously labelled as **cryptogenic cirrhosis**.

Approximately **20%** of NASH will develop **cirrhosis** and its associated complications.

### Features:

- Usually asymptomatic
- Hepatomegaly
- ALT is typically greater than AST
- Increased echogenicity on ultrasound

### Associated factors:

- 1) Obesity
- 2) Hyperlipidaemia
- 3) Type 2 DM
- 4) Jejunioileal bypass
- 5) Nutritional status: sudden weight loss/starvation or over-nutrition & TPN
- 6) Drugs (e.g., amiodarone, methotrexate)
- 7) Metabolic abnormalities (e.g. galactosaemia, glycogen storage diseases).

### Management:

- The mainstay of treatment is **lifestyle changes** (particularly weight loss, low fat and low calories diet) and monitoring: supervised exercise program with group weight loss counselling.
- There is ongoing research into the role of gastric banding and insulin-sensitising drugs (e.g. **Metformin**).
- Data from small clinical trials using **pioglitazone** have shown modest improvement in liver biopsy appearance over one year also **Orlistat** can reduce hepatic fat, although neither is licensed for the ttt of hepatic steatosis.

**Weight loss of 1 kg/week** with an initial target **loss of 10% body weight** has been shown to be effective at restoring normal liver function.

Rapid weight loss has been shown to increase fat deposition in the liver and may precipitate NASH.

Obese T2DM with abnormal LFTs >>>>- ? non-alcoholic fatty liver disease

- By far the most likely diagnosis in an obese type 2 DM is non-alcoholic fatty liver disease. This patient will require a liver screen, ultrasound and **liver biopsy** to confirm the diagnosis.
- A normal **ferritin** makes a diagnosis of **haemochromatosis** unlikely, although **it should always be considered in patients with both abnormal LFTs and diabetes.**

### In alcoholic hepatitis:

**DF (Discriminant Factor)** used to identify patients at high risk of mortality and to select patients for corticosteroid therapy.

$DF = 4.6 \times (\text{prothrombin time} - \text{control}) + \text{Bilirubin (mg/dl)}$ .

**DF > 32** indicates a one month mortality of 50%.

**The new Glasgow Alcoholic Hepatitis Score:** based on age, serum bilirubin, BUN, Prothrombin time, peripheral blood TLC: has recently been shown to be a better scoring system in predicting mortality.

### NB: In alcoholic hepatitis:

1) The **AST** is raised **more** than the ALT typically with a ratio of at least **2:1**.

2) **Macrocytosis** (high MCV).

3) Impaired **synthetic** function of liver (low albumin, elevated INR).

4) **Markedly raised IgA** and can cause mildly raised IgG and IgM.

If ALT is > 300 U/L you may suspect drug-induced, viral hepatitis, autoimmune hepatitis and ischaemic hepatitis.

**Raised IgA** can also be present in chronic active hepatitis and IgA nephropathy.

**Deficiency of IgA** produces autoimmune disorders, chronic diarrhoea and respiratory infections.

**Raised IgM** may be seen in primary biliary cirrhosis, Waldenström's macroglobulinaemia and infections.

**Reduced IgM** may be acquired or congenital and can be associated with myeloma.

**Raised IgE** in asthma, allergic Broncho pulmonary aspergillosis (ABPA), atopic dermatitis, psoriasis and parasitic diseases.

## Autoimmune hepatitis

Autoimmune hepatitis is condition of unknown aetiology which is most commonly seen in **young females (30-50 years)**.

Recognised associations include **other autoimmune disorders** such as **ulcerative colitis**, **Hashimoto thyroiditis**, **keratoconjunctivitis sicca**, **RA** and **peripheral neuropathy**.

It is also associated with **Hypergammaglobulinaemia**.

Diagnosis and prognostic assessment is best informed by liver biopsy.

60% are associated with HLA-B8, DR3 and Dw3.

Three types of autoimmune hepatitis have been characterised according to the types of circulating antibodies present.

Type I	Type II	Type III
Anti-nuclear antibodies ( <b>ANA</b> ) and/or anti-smooth muscle antibodies ( <b>SMA</b> )	Anti-liver/kidney microsomal type 1 antibodies ( <b>LKM1</b> )	Anti-Soluble liver- kidney antigen ( <b>SLA</b> )
Affects both adults and children	Affects <u>children only</u>	Affects adults in middle-age

**Features:**

- **Acute** hepatitis: fever, jaundice etc. (only **25%** present in this way).
- May present with signs of **chronic liver disease**: hepatosplenomegaly, deranged liver function with a low albumin, prolonged INR and evidence of extensive hepatic necrosis.
- Features of **cirrhosis** occur in around **75%** of cases.
- **Amenorrhoea** (common).
- The **sicca syndrome** (xerostomia, dry eyes, keratoconjunctivitis sicca) may occur.
- ANA/SMA/LKM1 antibodies.
- Raised **IgG** levels with normal IgA and IgM (although may be some ↑ IgM).
- **Liver biopsy**: the investigation of choice to **confirm** the diagnosis: inflammation extending beyond limiting plate 'piecemeal necrosis', bridging necrosis.

Autoimmune hepatitis is not usually present as an acute hepatitis (only 25%).

25% present as acute hepatitis but usually the onset is insidious.

Some may be asymptomatic for years and then are found to have signs of chronic liver disease.



### Management

- Steroids and other immunosuppressant e.g. azathioprine and cyclosporine (a maintenance therapy of prednisolone 10 mg + azathioprine 50 mg daily).
- Liver transplantation.

### NB:

- The combinations of **deranged LFTs** combined with **secondary amenorrhoea** in a **young female** strongly suggest autoimmune hepatitis.
- You should think of autoimmune hepatitis after exclusion of other causes of hepatitis such as viral, alcohol and drugs.
- Smooth muscle antibodies (SMA) are associated with autoimmune hepatitis. Presentation is usually insidious and extra hepatic clinical features are common.

### Hepatitis C

Hepatitis C is likely to become a significant public health problem in the UK in the next decade. It is thought around 200,000 people are chronically infected with the virus. At risk groups include intravenous drug users and patients who received a blood transfusion prior to 1991 (e.g. haemophiliacs).

### Transmission:

- The risk of transmission during a needle stick injury is about **2%**
- The risk of transmitting the virus during sexual intercourse is probably less than **5%**
- The vertical transmission rate from mother to child is about **6%**
- Elective caesarean section does not reduce the risk of transmission.
- Breast feeding is not contraindicated in mothers with hepatitis C.
- Ribavirin is teratogenic and there is little clinical data about how well this or interferon is tolerated in pregnancy.
- Children under 1 year can be tested for hepatitis C, but as there is transmission of the antibodies from the mother they may test positive with respect to serology in the first year.

About **6** out of every **100** infants born to **HCV-infected women** become **infected**. This occurs at the time of **birth** and this is **no** way of preventing this.

### Features:

- After exposure to the hepatitis C virus less than 20% of patients develop an acute hepatitis.
- Around 85% of acute hepatitis C infections lead to chronic infection.
- Acute hepatitis C has a good response to ttt if started early.

### Complications:

- Chronic infection (80-85%) - only 15-20% of patients will clear the virus after an acute infection and hence the majority will develop chronic hepatitis C.
- Cirrhosis (20-30% of those with chronic disease)
- Hepatocellular cancer
- Cryoglobulinaemia

### Extra-hepatic associations with HCV:

- 1) **Sjogren's** syndrome.
- 2) **Porphyria cutanea tarda**, rather than acute intermittent porphyria.
- 3) **Lichen planus**, rather than lichen sclerosis.
- 4) **Cryoglobulinaemia** (mixed essential type).
- 5) **Lymphoma**, rather than leukaemia
- 6) **Myeloma** and **monoclonal gammopathies**, rather than Waldenström macroglobulinaemia.

### Management of chronic infection:

- Treatment with interferon alpha alone has around a 10-15% success rate in achieving long term undetectability of plasma hepatitis C RNA.
- Currently a **combination** of pegylated interferon-alpha and ribavirin are used.
- Up to 55% of patients successfully clear the virus, with success rates of around 80% for some strains.
- Response to therapy is determined by normalisation of hepatic transaminases and undetectability of hepatitis C RNA in plasma.
- The aim of treatment is sustained virological response (SVR), defined as undetectable serum HCV RNA 6 months after the end of therapy.
- HCV genotype will give guidance to the **length of treatment** and **response rate**:
  - Those with genotype **2** and **3** can achieve SVR after **24** weeks, as they have a far **better** response to ttt than genotype 1 & 4.
  - In genotype **1** and **4**, antiviral is continued for **48** weeks due to **lower** response rate.

- **Liver biopsy** provides histological activity indices to help quantify the degree of inflammation and fibrosis and is generally **only** indicated in those with genotype 1 and 4, as ttt is longer.

### Complications of treatment:

- **Interferon alpha** - side-effects: flu-like symptoms, depression, fatigue, leukopenia, thrombocytopenia.
- **Ribavirin** - side-effects: haemolytic anaemia, cough. Women should not become pregnant within 6 months of stopping ribavirin as it is teratogenic.

### NB:

- Acute hepatitis C infection is asymptomatic in 60-70% of cases, infection is chronic in around 85% of individuals.
- So, **No HCV vaccine** is available.
- But treatment is successful in around 50% of patients.
- Hepatitis C >>>>> 80-85% become chronically infected.
- Liver cirrhosis >>>>will develop in around 20-30% of patients over 20-30 years.
- Presence of HCV Ab indicates old exposure to the virus, if detected a viral RNA load is required to determine whether there is active infection.
- Persistence of viral RNA in the bloodstream more than 6 months after exposure (or acute illness if symptoms develop) indicates chronic HCV infection.

The following also predict a good long term response to interferon:

- Younger age.
- Female gender
- Non-black racial origin
- Low hepatic iron
- Absence of cirrhosis on biopsy

### **Hepatitis B**

Hepatitis B is a double-stranded DNA virus and is spread through exposure to infected blood or body fluids, including **vertical transmission** from mother to child. The incubation period is 6-20 weeks.

**Perinatal transmission** is the **most common route** of HBV infection - the infection rate is **90%** in infants born to **HBeAg positive mothers**.

Blood inoculation through unclean needles is **not** the commonest route of transmission of hepatitis B but this remains important.

Sexual transmission comprises 30% of HBV infections in developed countries.

**Hepatitis B serology:**

Interpreting hepatitis B serology is a dying art form which still occurs at regular intervals in medical exams. It is important to remember a few key facts:

- HBsAg is the first marker to appear and causes the production of HBsAb.
- The presence of HBsAg in the serum is indicative of active HBV infection, either acute or chronic.
- HBsAg normally implies acute disease (present for 1-6 months).
- If HBsAg is present for > 6 months then this implies chronic disease (i.e. Infective) (i.e. a carrier).
- HBsAb implies immunity (either exposure or immunisation). It is negative in chronic disease.
- Anti-HBc implies previous (or current) infection. IgM anti-HBc appears during acute or recent hepatitis B infection and is present for about 6 months. IgG anti-HBc persists for long life. (HBcAb IgG = وصمة العار)
- HBcAb IgG is produced from around 14 weeks after exposure, in the absence of HBcAb IgM it may indicate cleared or chronic HBV infection.
- HBeAg results from breakdown of core antigen from infected liver cells as is therefore a marker of infectivity and replication.
- HBeAg negativity implies that the patient no longer has active infection.
- HBeAg is present in acute infection and may persist in chronic for several years.
- The phenomenon of loss of HBeAg and seroconversion to HBeAb positive status indicates a reduction of inflammation accompanied by histological change from active to inactive hepatitis.
- **HBeAg is a marker of infectivity in all patients except those who have HBV with pre-core mutant, because they don't synthesize HBeAg, this is most commonly due to stop-codon mutation at nucleotide 1896. So the learning point here is that **although HBeAg is negative some patients still may have active HBV and is still infective.****

So not all negative HBeAg are not infective, may be <b>HBV with pre-core mutant</b> (negative HBeAg but still infective).
---

<b>Active HBV infection means any detectable DNA in blood &gt;&gt;&gt; need TTT.</b>
--

Common example results:

- **Previous immunisation:** anti-HBs positive, all others negative.
- **Previous hepatitis B (> 6 months ago), not a carrier (= cleared):**  
anti-HBc IgG positive, HBsAg negative.
- **Previous hepatitis B, now a carrier (= chronic hepatitis):**  
anti-HBc IgG positive, HBsAg positive.

**NB:** The presence of **isolated HBcAb** signifies one of 3 possibilities:

- 1) The patient is in the period of acute hepatitis B between the disappearance of the HBsAg and the appearance of HBsAb.
- 2) HBsAb has fallen to undetectable levels following recovery from acute hepatitis B.
- 3) Chronic HBV infection where the HBsAg titre has fallen to undetectable levels.

**NB:** Patients who are positive for HBsAg for more than 6 months but are HBeAg negative, HBV DNA negative and have normal ALT >>> do **not** require liver biopsy **nor** do they require antiviral therapy, only hepatitis B serology and ALT should be **monitored** annually.

### Immunisation against hepatitis B:

- Contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using **recombinant DNA technology**.
- Most schedules give 3 doses of the vaccine with a recommendation for a one-off booster 5 years following the initial primary vaccination.
- At risk groups who should be vaccinated include: healthcare workers, IV drug users, sex workers, and close family contacts of an individual with hepatitis B, individuals receiving blood transfusions regularly, chronic kidney disease patients who may soon require renal replacement therapy, prisoners, and chronic liver disease patients.
- Around 10-15% of adults fail to respond or respond poorly to 3 doses of the vaccine. Risk factors include age over 40 years, obesity, smoking, alcohol excess and immunosuppression.
- Testing for anti-HBs is only recommended for those at risk of occupational exposure (i.e. Healthcare workers) and patients with chronic kidney disease. In these patients **anti-HBs levels** should be **checked 1-4 months after** primary immunisation.
- The table below shows how to interpret anti-HBs levels:

Anti-HBs level (mIU/ml)	Response
> 100	Indicates adequate response, no further testing required. Should still receive booster at 5 years.
10 – 100	Suboptimal response - one additional vaccine dose should be given. If immunocompetent no further testing is required.
< 10	Non-responder. Test for current or past infection. Give further vaccine course (i.e. 3 doses again) with testing following. If still fails to respond then HBIG would be required for protection if exposed to the virus.

**Complications** of hepatitis B infection:

- Acute fulminant hepatitis with acute liver failure (1%)
- Chronic hepatitis (5-10%)
- Hepatocellular carcinoma
- Membranous glomerulonephritis
- Cryoglobulinaemia
- Polyarteritis nodosa

Deterioration in patient with hepatitis B >>>>- ? hepatocellular carcinoma

**Management** of hepatitis B:

- **Pegylated interferon-alpha** used to be the only treatment available. It reduces viral replication in up to 30% of chronic carriers. A better response is predicted by being female, < 50 years old, low HBV DNA levels, non-Asian, HIV negative, high degree of inflammation on liver biopsy. It is used in chronic HBV with positive HBeAg.
- However due to the **side-effects** of pegylated interferon it is now used **less** commonly in clinical practice.
- Interferon **cannot** be used in **decompensated** liver cases (ascites, portal hypertension, low serum albumin, high INR, etc.) as it can **initially worsen hepatic decompensation**.

- **Oral antiviral** medication is increasingly used with an aim to suppress viral replication (not in dissimilar way to treating HIV patients) Examples include: **Entecavir**, **Tenofovir** and **Lamivudine**.
- **Entecavir** or **Tenofovir** would be **the most appropriate drug** choice. In certain circumstances the two may even be combined. Their use in this situation is not risk free and may precipitate a lactic acidosis so careful monitoring is required.
- They are **second** line to interferon for **compensated** liver disease, but with hepatic **decompensation**, they are a reasonable **first** choice.
- **Lamivudine** alone is safe in **decompensated** HBV infection however it is **no** longer the drug of choice in this setting as entecavir and tenofovir give more rapid control of HBV DNA levels. Additionally lamivudine resistance may be pre-existent or induced.
- **Liver biopsy** is **only** indicated in patients who have **elevated liver enzymes** and **positive HBeAg**.
- Antiviral therapy of HBV is indicated for **progressive liver disease** as manifested by **histological** evidence of active **inflammation ± fibrosis**. The best results are seen in **HBeAg positive** patient with **elevated liver enzymes**.
- Guidance suggests in a case of HBV, it is worth offering **HIV** and **HCV** tests as exposure to HBV may well indicate exposure to other blood borne viruses.

#### Hepatitis B and pregnancy

##### Basics:

- All pregnant women are offered screening for hepatitis B.
- Without intervention the vertical transmission rate is around 20%, which increases to 90% if the woman is positive for HBeAg.
- **HBeAg** is present in the **acute** phase and indicates a **highly infectious state**.
- Babies born to mothers who are chronically infected with hepatitis B or to mothers who've had acute hepatitis B during pregnancy should receive a complete course of vaccination + hepatitis B immunoglobulin.
- Studies are currently evaluating the role of oral antiviral treatment (e.g. Lamivudine) in the latter part of pregnancy.
- There is little evidence to suggest caesarean section reduces vertical transmission rates.
- Hepatitis B cannot be transmitted via breastfeeding (in contrast to HIV).

The most common causes of an **acute severe** liver injury in a **young woman** are:

- 1) **Viruses** (including HAV, HBV).
- 2) **Drugs** (particularly **paracetamol** overdose).
- 3) **Ischemic hepatitis.**
- 4) **Autoimmune hepatitis.**
- 5) **Hepatic vein thrombosis (Budd-Chiari syndrome [BCS]):** (often precipitated by pregnancy or oral contraceptive pill [OCP] use or Antiphospholipid syndrome).

The presence of liver failure, ankle oedema, and an exudative ascites do not help differentiate between these aetiologies.

**Tender hepatomegaly** is one of the hallmarks of **BCS**.

### Chronic active hepatitis

20% of patients with HBV will develop chronic active hepatitis, whereas the incidence is **higher 50%** in **HCV** infection.

It is usually due to old history of blood transfusion.

The aminotransferase and bilirubin are **mildly raised**.

The histological landmark is **piecemeal necrosis**.

Causes of chronic active hepatitis:

- **Viral**.
- Autoimmune (anti LKM ab).
- Drugs (Aldomet, INH).
- Alpha-1-antitrypsin deficiency.
- Ulcerative colitis (UC)

### Hepatitis E

Overview:

- RNA virus.
- Spread by the faecal-oral route, **incubation period = 3-8 weeks**.
- Common in Central and South-East Asia, North and West Africa, and in Mexico.



- Causes a similar disease to hepatitis A, but carries a significant mortality (about 20%) during pregnancy.
- Does not cause chronic disease
- A vaccine is currently in development, but is not yet in widespread use.

NB: Male homosexuality is a recognized risk factor for hepatitis A infection, anal intercourse is a likely route of enteral transmission.

#### Child-Pugh Classification of liver cirrhosis

It is a scoring system to assess the severity of liver cirrhosis.

Score	1	2	3
Bilirubin ( $\mu\text{mol/l}$ )	<34	34-50	>50
Albumin (g/l)	>35	28-35	<28
Prothrombin time, prolonged by (s)	<4	4-6	>6
Encephalopathy	none	mild	marked
Ascites	none	mild	marked

Summation of the scores allows the severity to be graded either A, B or C:

- < 7 = A
- 7-9 = B
- > 9 = C

#### Notes about liver cirrhosis:

The hepatic stellate cells which reside in the space of Disse are central to the process of fibrosis within the liver i.e. **the final common pathway of hepatic fibrosis** is mediated by the **hepatic stellate cell**.

**TNF- $\alpha$**  is a pro-inflammatory effector in fibrotic liver injury, through activation of the stellate cells. These cells then secrete the fibrillar collagen constituting the **defining features of hepatic fibrosis**.

**IL-10** is thought to exert **anti-inflammatory effects** on the stellate cell.

**Endothelin** is a **vasoconstrictor** in the hepatic sinusoids (similarly in the endothelium of the systemic circulation) and functions by causing contraction of the hepatic stellate cells thus increasing intrahepatic sinusoidal resistance and **promoting portal hypertension**.

**Nitric oxide** antagonises the effects of Endothelin in the liver.

**The 5 year survival after liver transplantation** is now **75%**.

Patients with cirrhosis are frequently **hyponatraemic**.

- This is a function of an **inability to excrete free water** (increased ADH levels and systemic vasodilation contribute, but the underlying mechanism is complex and not entirely understood).

- **Secondary hyperaldosteronism** will result in total body sodium overload but **not necessarily hyponatraemia**.

- Remember that the Na level is a concentration, therefore if the amount of solvent (water) is increased then it will not necessarily rise.

- The development of **ascites** is related to this process but is not the cause of dilution, i.e. **Ascites is due to reduced urinary Na excretion**.

There is **increased** plasma volume and **decreased** vascular resistance.

**The British Society of Gastroenterology (BSG) guidelines on the management of ascites:**

**EX:** Alcoholic patient with a significantly distended abdomen with shifting dullness >>> the most appropriate **first-line treatment** for his ascites is >>> **Paracentesis**.

The treatment of choice for **large, symptomatic** ascites is >>> **large volume therapeutic paracentesis**.

If the volume of ascites is **not** sufficient to warrant paracentesis then **first** line treatment is **dietary salt restriction** (to no more than 90 mmol/day) and **spironolactone**.

Initial dose of spironolactone in this setting is **100 mg/day** and may be titrated **up to 400 mg/day**.

**Once** the maximum dose of spironolactone has been reached, **furosemide** can be added if there is still significant ascites accumulation and the renal function and electrolytes will tolerate further diuresis.

Doses of furosemide are advised start at **40 mg/day** titrating **up to 160 mg/day** as tolerated or needed.

Furosemide alone has poor efficacy in cirrhosis.

Indications of **TIPSS** are:

- Diuretic resistant ascites
- Intractable portal hypertensive bleeding and
- Hepato-renal failure.

Patients with chronic liver disease and ascites often develop hyponatraemia, the management of which can be difficult.

Diuretic therapy for the management of ascites often contributes to the hyponatraemia.

The **British Society of Gastroenterology** guidelines suggest that where the **serum Na is  $\leq 120$  mmol/L >>> diuretic therapy should be stopped and give the patients volume expansion with colloid or normal saline.**

No specific intervention other than careful **monitoring** is advised where the serum sodium is **126-135** mmol/L.

In the range **121-125** mmol/L where the serum creatinine is normal, **diuretic** therapy may be continued but may need to be **reduced** with a view to stopping if necessary.

If the sodium is in this range but the serum creatinine is rising diuretics should be stopped and patients should receive volume expansion.

These guidelines also advise that **fluid restriction** should only be used in patients who are clinically **euvolaemic**, **not on diuretics** and have severe hyponatraemia with a normal serum creatinine.

**EX:** Pt. with CLD and ascites on diuretics with serum Na 115 mmol/L >>> **Stop diuretics and give normal saline.**

**Lactulose:**

It is an osmotic laxative, it is used in patients with cirrhosis/hepatic encephalopathy to **limit the proliferation of ammonia-forming gut organisms** and **increase the clearance of protein load in the gut**.

Dose of lactulose **30-50 ml / 6hrs** orally or via nasogastric tube.

It causes **hypomagnesaemia** associated with diarrhoea.

It is **not absorbed** It does not affect the absorption of spironolactone and

It may be used in diabetics.

Pt with chronic **HCV** infection + **renal failure** + significant **proteinuria** + high urine Na + relative hypertension >>> **cryoglobulinaemia**

Hepatitis C infection is strongly associated with **mixed essential cryoglobulinaemia** which may produce **mesangiocapillary** (also known as **membranoproliferative**) glomerulonephritis.

This condition is associated with renal impairment, systemic vasculitic manifestations (including neuropathy, skin manifestations) and arterial thrombosis.

**Liver biopsy in cirrhosis:**

- Fibrous septa formation
- Subendothelial fibrosis
- Liver cell necrosis
- Nodular regeneration

In the **micronodular** form, the nodules are **less than 3 mm** across with uniform liver involvement - seen in **alcohol** or **biliary** disease.

In the **macro nodular** form there are larger nodules, classically seen in **chronic viral hepatitis**.

In patients with **liver cirrhosis**, there is **false positive elevated level** of **CA-125** as high as 30-80%.

So, **CA-125** is done in conjugation with **abdominal US**.

So female patient with liver cirrhosis and high CA-125, not mandatory means that she has ovarian carcinoma.

In women where there is a family history of ovarian carcinoma, **genetic screening** for **BRCA 1 and 2** is recommended as the preferred method for assessing future ovarian carcinoma risk.

### Hepatic encephalopathy:

There are **5 grades** of hepatic encephalopathy:

- 1) **Grade 0:** include **minimal** alterations and impairment of executive function.
- 2) **Grade 1:** patients are **drowsy**, is associated with **sleep** abnormalities (typically sleep inversion) and changes to **behaviour** and **personality** (irritability, poor concentration).
- 3) **Grade 2:** **Lethargy, apathy** and **drowsiness** are features of grade 2.
- 4) **Grade 3:** depressed conscious levels (but arousable).
- 5) **Grade 4:** patients are **comatose** with no response to painful stimuli.

There is **little** evidence for the role of **protein restriction** in hepatic encephalopathy. This may exacerbate the condition as these patients are often malnourished.

### Hepatorenal syndrome (HRS)

#### The diagnostic criteria for HRS:

- 1) **Acute** or **chronic** hepatic disease with advanced **hepatic cell failure** and **portal hypertension**.
- 2) Serum **creatinine** concentration **> 133 Mmol/L** that progresses over days to weeks.
- 3) **Absence of any other apparent cause** for the renal disease like shock, sepsis, nephrotoxic drugs, and the absence of US finding of obstruction of parenchymal renal disease.
- 4) It is important to **exclude SBP**, which is complicated with acute renal failure.
- 5) **Urinary Na below 10 mEq/l** (off diuretics).
- 6) **Urinary protein excretion below 500 mg/day**.
- 7) **Lack of improvement** in renal function after volume expansion with 2 litres of normal saline.

Hepatorenal syndrome has been categorized into two types:

Type 1 HRS شرس	Type 2 HRS
<ul style="list-style-type: none"> <li>• Rapidly progressive.</li> <li>• Doubling of serum Creatinine to <math>&gt; 221 \mu\text{mol/L}</math> or a halving of the Creatinine clearance to less than 20 ml/min over a period of less than 2 weeks.</li> <li>• Very poor prognosis.</li> </ul>	<ul style="list-style-type: none"> <li>• Slowly progressive.</li> <li>• Prognosis poor, but patients may live for longer.</li> </ul>

The management of hepatorenal syndrome (HRS) is notoriously difficult.

The ideal treatment is liver transplantation but patients are often too unwell to have surgery and there is a shortage of donors.

#### Management options:

- 1) **Vasopressin** V1 receptors agonist, for example **terlipressin**, have a growing evidence base supporting their use. They work by causing vasoconstriction of the splanchnic circulation, which may reverse the early splanchnic vasodilatation seen in HRS.
- 2) Volume expansion with **20% albumin** (1.5 gm/ Kg of body weight at diagnosis and 1.0 gm/ kg 48 hours later).
- 3) **Antibiotics**, has been shown in RCT to markedly reduce the risk of hepatorenal syndrome.
- 4) Transjugular intrahepatic portosystemic shunt (**TIPS**).
- 5) **Liver transplantation**.

Small studies with dopamine have shown no renal benefit in such patients.

No evidence exists for the use of dobutamine or Octreotide.

#### **Hepatopulmonary syndrome (HPS)**

This is characterised by an **oxygenation defect** induced by **pulmonary vascular dilatation** in patients with liver cirrhosis or portal hypertension.

This oxygenation defect consists of a **wide alveolar-arterial gradient** (AAG) ( $>15\text{mmHg}$ ). The vascular dilatation is thought to be induced by increased pulmonary levels of nitric oxide. It is seen in **15-30% of patients with cirrhosis** and is a poor prognostic indicator.

Most patients with hepatopulmonary syndrome are **asymptomatic** or have dyspnoea with an insidious onset. Dyspnoea whilst **standing (platypnoea)** and hypoxemia exacerbated by being **upright (orthodeoxia)** are characteristic, and are thought to be due to the **predominance** of **vascular dilatation** in the **lung bases**. Blood flow to these areas is increased in the upright position.

Desaturation during sleep is also often seen as are clubbing and cyanosis.

**Contrast-enhanced transthoracic echocardiography** is the best test to demonstrate **intrapulmonary vascular dilatation**. It can also exclude **intracardiac shunting** which may result in similar signs and symptoms to hepatopulmonary syndrome.

This is performed by injecting agitated saline IV during transthoracic echocardiography.

- In a **normal** subject microbubbles are visualised in the right ventricle within seconds, which are then absorbed in the alveoli.
- Immediate visualisation in the **left** ventricle (within 3 cardiac cycles) indicates **intracardiac** shunting.
- Delayed visualisation in the left ventricle (3-6 cardiac cycles) is diagnostic of **intrapulmonary** shunting.

Chest radiographs can be normal or show non-specific interstitial changes.

ABGs should be taken in the sitting position to grade the severity of the condition based on the degree of hypoxemia.

**Liver transplantation** is the only proven beneficial available treatment, with 85% of patients showing resolution or significant improvement in gas exchange postoperatively.

### Hepatocellular carcinoma (HCC)

HCC is the third most common cause of cancer worldwide.

- **Chronic hepatitis B is the most common cause of HCC worldwide**
- **While, chronic hepatitis C being the most common cause in Europe.**

The main risk factor for developing HCC is liver cirrhosis, for example secondary to hepatitis B & C, alcohol, haemochromatosis and primary biliary cirrhosis.

Other risk factors include:

- Alpha-1 antitrypsin deficiency
- Hereditary tyrosinosis

- Glycogen storage disease
- Aflatoxin
- Drugs: oral contraceptive pill, anabolic steroids
- Porphyria cutanea tarda
- Male sex
- DM, metabolic syndrome

\*Wilson's disease is an exception

### Features:

- Tends to present late
- Features of liver cirrhosis or failure may be seen: jaundice, ascites, RUQ pain, hepatomegaly, pruritus, splenomegaly
- Possible presentation is decompensation in a patient with chronic liver disease

**Screening** with ultrasound (+/- alpha-fetoprotein) should be considered for high risk groups such as:

- Patients with liver cirrhosis secondary to hepatitis B & C or haemochromatosis.
- Men with liver cirrhosis secondary to alcohol.

### Management options:

The only proven potentially curative therapy for HCC remains **surgical**, either **hepatic resection** or **liver transplantation**.

- **Hepatic resection** should be considered as a primary therapy in any patient with HCC and **non-cirrhotic** liver.
- **Liver transplantation** should be in any patient with **cirrhosis** and a **single small HCC < 5 cm** or **multiple up to 3 lesions < 3 cm**.
- Non-surgical therapy is **only** used when **surgical therapy is not** possible and with **extra hepatic dissemination**.
- **Percutaneous ethanol injection** has been shown to produce necrosis of **small HCC** and is best used in **peripheral** lesions.
- **TACE** can produce tumour necrosis and has been shown to affect survival in highly selected patients with good liver reserve.
- **Radiofrequency ablation (RF)**.
- Systemic chemotherapy has a poor response rate.
- Hormonal therapy like tamoxifen has no survival benefit in controlled trials.
- **Sorafenib**: a multikinase inhibitor.
- Interferon has been used as ttt of HCC rather than the underlying viral infection, but remains controversial.



### Spontaneous bacterial peritonitis (SBP)

SBP is a form of peritonitis usually seen in patients with ascites secondary to liver cirrhosis.

SBP occurs in around **8% of cirrhotic patients with ascites**.

SBP has **poor** prognostic significance with **high mortality** as a **one** year survival after a diagnosis of between **30-50%** and **recurs** in **70%** of patients **within one year**.

An **episode** of SBP carries a 2 year mortality rate of **50%**.

It is, as the name suggests a spontaneous event that is not a consequence of intestinal perforation.

It is speculated that the infective organism may leak into the ascitic fluid via the blood or from intestinal overgrowth.

Organisms should be cultured by directly collecting into blood culture bottles.

It is typically caused by **aerobic** gram **negative** bacteria.

Hence, antibiotics such as co-amoxiclav, Tazoscin or ciprofloxacin are typically used as first line treatment.

**E. coli, Klebsiella** and **Enterococci** should be considered **aerobic** organisms. They are more precisely defined as **facultative anaerobes**, that is to say they reproduce best in aerobic conditions but can also reproduce in anaerobic conditions.

**SBP** is usually the result of infection with a **single organism**, almost invariably **Gram negative**.

But the **polymicrobial** nature (**both** Gm +ve and Gm – ve) of this infection makes **perforated abdominal viscera** the most likely diagnosis.

**Diagnosis:** Paracentesis >>> **Neutrophil count (PMN) > 250 cells/mm<sup>3</sup>**

#### Management:

- IV cefotaxime is usually given.
- Patients who have had an episode of SBP should be on prophylactic antibiotics (Norfloxacin is recommended for short term prophylaxis).

Alcoholic liver disease is a marker of poor prognosis in SBP.

Spontaneous bacterial peritonitis (SBP) >>> IV cefotaxime

### Primary biliary cirrhosis (PBC)

Primary biliary cirrhosis is a chronic liver disorder typically seen in middle-aged **females 40-70 years** (female: male ratio of 9:1). (**90%** of cases **female**)

The aetiology is not fully understood although it is thought to be an **autoimmune** condition.

There is strong **association with other autoimmune conditions** (see later).

PBC is associated with **HLA-DR3** and **HLA-DR8**.

It is characterised by portal inflammation and immune-mediated **gradual destruction** of the **intrahepatic** bile ducts which results in reduced bile secretion and retention of toxic substances. This leads to further hepatic damage, fibrosis and **cirrhosis**.

Interlobular bile ducts become damaged by a chronic inflammatory process causing progressive cholestasis which may eventually progress to cirrhosis.

The classic presentation is **itching** in a **middle-aged woman**.

PBC is characterised by **ant mitochondrial antibodies (AMA) (M2)**, which are present in **90-95%** of patients (often before clinical signs develop) and have a **specificity** of **98%**.

**Positive AMA + ↑ ALP + Dyslipidaemia >>> strongly suggestive of BPC.**

#### Clinical features:

- Early: 50% of patients may be **asymptomatic** at diagnosis (e.g. raised **ALP** and GGT on routine LFTs) or mainly **Lethargy (fatigue)**, **pruritus** before jaundice.
- **Lethargy** is the most common symptom (**70%**) followed by **pruritis**.
- Cholestatic **jaundice**
- **Hypercholesterolemia**, **Xanthelasmas**, xanthomata
- Hyperpigmentation, especially over pressure points: dermatitis herpetiformis.
- Also: clubbing, hepatosplenomegaly and portal hypertension
- Late: may progress to liver failure

In PBC, **once jaundice develop** survival is less than **2 years** and criteria for **transplantation** is **high bilirubin > 100 Mmol/L** and **intractable pruritis**.

The median survival **overall** is **7-10 years** ☹

But reduced to **less than 2 years** in the presence of **jaundice** ☹

The 5 years survival **post-transplant** is about **70-80%**.

**Associations:**

- 1)  Sjogren's syndrome (SS) (seen in up to 80% of patients)
- 2)  Rheumatoid arthritis (RA)
- 3) Systemic sclerosis (SS) and CREST syndrome.
- 4)  Thyroid disease
- 5) Membranous GN.
- 6) RTA

**Diagnosis:**

- 1) Anti-mitochondrial antibodies (AMA) **M2** subtype titre > 1:40 is present in **98%** of patients (often before clinical signs develop) and is **highly specific** have a **specificity of 98%**.
- 2) Smooth muscle antibodies (SMA) in 30% of patients.
- 3) Raised serum IgM.

**Complications:**

- **Malabsorption of fat-soluble vitamins (A,K,E,D)** is common: **osteomalacia, coagulopathy** (bruising).
- **Sicca** syndrome occurs in **80%** of cases.
- Portal hypertension: ascites, variceal haemorrhage.
- Hepatocellular cancer (**20-fold increased risk**)
- In symptomatic patients **median** survival is approximately **5 years** without transplantation.
- Overall, survival from time of diagnosis is put at between **7-17 years**.

**Management:**

- 1) **Ursodeoxycholic acid**: it improve liver biochemistry and delays disease progression.
- 2) Pruritus: cholestyramine.
- 3) Fat-soluble vitamin supplementation.
- 4) **Liver transplantation** is the inevitable late ttt of choice especially if bilirubin > 100 (PBC is a major indication of liver TX.) - Recurrence in graft can occur in up to 16% of cases after 5 years but is not usually a problem.

Liver transplantation is very effective in PBC - the 5 year survival is **>80%**.

**NB:** The **two main** conditions causing pigmentation and chronic liver disease are: primary biliary cirrhosis (**PBC**) and **haemochromatosis**.

### Primary sclerosing cholangitis (PSC)

Primary sclerosing cholangitis is a **chronic cholestatic liver** disease of **unknown** aetiology characterised by inflammation and fibrosis of intra and extra-hepatic bile ducts.

Around 70% of patients diagnosed with PSC are **men**, with an average age of around 40 years.

Time from diagnosis to end-stage hepatic failure is thought to be around 12 years.

Colectomy has no the nature history of PSC development at all.

#### Associations:

- **Ulcerative colitis (UC):** 4% of patients with UC have PSC, up to 90% of patients with PSC have UC.
- Crohn's (much less common association than UC)
- HIV

4% of patients with UC have PSC and 80% of patients with PSC have UC
--

#### Features:

- Cholestasis: jaundice and pruritus
- Right upper quadrant pain
- Fatigue
- Weight loss
- FUO

#### Investigation:

- **ERCP** is the gold standard diagnostic tool, showing multiple intrahepatic and extra hepatic bile duct strictures and dilatations, giving a '**beaded**' appearance.
- However the non-invasive magnetic **MRCP** is often performed initially, MRCP would be the initial diagnostic investigation of choice particularly given a lower complication rate and its ability to image ducts proximal to obstructing strictures.
- Increase in **IgM** in 84 % of cases.
- **P-ANCA** may be positive in 65-85% of cases.
- Positive **ANA** in 55% of cases
- There is a limited role for liver biopsy, which may show fibrous, obliterative cholangitis often described as 'onion skin'.
- Ultrasound may be normal in up to 50% of cases in early stages.

**PSC:**

The **gold standard** diagnostic tool >>> **ERCP**,

The **initial** diagnostic investigation of choice >>> **MRCP**

**Complications:**

- **Cholangiocarcinoma** (in 10-15% of PSC cases)
- Increased risk of colorectal cancer

**TTT: Liver transplantation:**

Survival post liver transplant is around 90%, although the chance of rejection is high.

High dose of ursodeoxycholic acid failed to show any benefit in PSC patients.

**NB:** Most patients with severe PSC are surveyed for the possible development of cholangiocarcinoma and are recommended for **liver transplantation before** this occurs.

But If there is **MRI cholangiography** evidence of cholangiocarcinoma with local lymphatic invasion >>> surgical removal is likely to be unsuccessful.

The ttt of choice in this occasion is **ERCP with stenting** of the lesion, it is successful at relieving symptoms of jaundice and may also relieve associated lethargy and fatigue.

Stent replacement may be required every 3-6 months, and adjuvant radiotherapy past stent placement may prolong survival for as long as 17 months.

**EX:** Pt with **PSC** and **develop cholangiocarcinoma** with **invasion** >>> **ERCP with stenting**.

**EX:** Male pt. known to have **ulcerative colitis** presented with **lethargy, itching, RUQ pain** and a blood picture consistent with obstructive liver disease (**cholestasis**)  
↑**ALP** >>> **Primary sclerosing cholangitis (PSC) / Cholangiocarcinoma** >>> **ERCP / MRCP**.

The most effective ttt is **liver transplantation**.

**Gilbert's syndrome**

Gilbert's syndrome is an **autosomal recessive** condition (although the exact mode of inheritance is still a matter of debate)

It is of defective bilirubin **conjugation** due to a deficiency of UDP glucuronyl transferase.

Gilbert's is the **most common** condition causing **mild isolated hyperbilirubinaemia** with all the other **LFTs** are completely **normal**.

The prevalence is approximately 2-7% in the general population.

It is often diagnosed incidentally during routine per-employee check-up.

The jaundice is usually **exacerbated** by periods of fasting, alcohol, acute illness even like sore throat also by oestrogen and it is **improved** by low dose barbiturates.

**Features:**

- **Unconjugated** hyperbilirubinaemia (i.e. not in urine).
- Jaundice may only be seen during an intercurrent illness.

**Investigation:** rise in bilirubin provoked by prolonged fasting or IV nicotinic acid.

**Management:**

- **No** treatment required.
- If severe jaundice (which is rare), phenobarbitone can rapidly decrease unconjugated serum bilirubin levels.

**EX:** A 26-year-old presents in the first trimester of her first pregnancy she feels well. Blood tests show a bilirubin of 40  $\mu\text{mol/L}$  (1-22); the other LFTs are completely normal >>> **Gilbert's syndrome**.

**EX:** Morning sickness and pruritus are common in pregnant women. An ALP of 160 U/l which is normal in a pregnant woman leaving the only abnormal result being the raised bilirubin (which usually falls in pregnancy). The most likely diagnosis is therefore **Gilbert's syndrome**.

**NB: Intrahepatic cholestasis of pregnancy (ICP):**

- It is caused by a bile acid transport defect.
- It is relatively common but usually occurs in the **second** or **third** trimester (it would not occur in the first trimester).
- It may be due to inherited susceptibility of liver cells to high oestrogen levels (a similar condition is seen in association with OCP use).
- **Itching** is the commonest symptom of ICP.
- **ALP (> 4 times)** and **GGT** is usually **high** with modest elevations in AST (< 300 IU/L) and bilirubin (< 100  $\text{Mmol/L}$ ).

- Risk increases with **multiparity**. It is more common in women with a history of cholestasis associated with **OCP** use and those who have a **family history** of ICP.
- There is an **increased risk of** foetal distress, preterm labour and perinatal death therefore careful foetal monitoring is essential.
- Long-term maternal outcome is relatively good compared to other liver conditions associated with pregnancy. **The prognosis is excellent** for the mother and the condition rapidly **resolve with 2-4 weeks after delivery** of the child. It may **recur in 40%** of cases.
- Prior to delivery, **antihistaminic**, **BDZs** and **ursodeoxycholic acid** have a role in symptom relief and sometimes **Vit K** if there is deranged clotting.

### **NB: Acute fatty liver of pregnancy (AFLP):**

- It is a condition of the **third** trimester, and is common in **first** and **multiple** pregnancies.
- The diagnosis is a **clinical** one and there is characteristically an **elevated TLC, low glucose, low albumin, raised NH<sub>3</sub> (ammonia)** level and evidence of **DIC** in up to **75%** (**prolonged INR, schistocytes** in blood smear).
- It is associated with abnormalities of the **synthetic** function, therefore serum **albumin** would be expected to be **low**.
- TTT:
  - **Protein restriction ± laxative** (to ↓ ammonia load).
  - **IV dextrose** to correct hypoglycaemia,
  - **FFP** to correct coagulopathy, followed by
  - **Expedition delivery** which results in dramatic recovery of the mother.
- The **HELLP** syndrome is associated with **preeclampsia** and there is a degree of overlap with **HUS/TTP**.

### **D.D: Pregnancy with deranged LFTs:**

- Hepatitis: viral A or autoimmune.
- HELLP
- Acute fatty liver of pregnancy (AFLP).
- Cholestasis of pregnancy.
- Budd-Chiari syndrome.

### **Dubin-Johnson syndrome (DJS)**

Dubin-Johnson syndrome is a rare benign autosomal recessive (AR) disorder of impaired bilirubin excretion resulting in mild jaundice but **normal liver function**. Resulting in conjugated hyperbilirubinaemia (therefore present in urine).

DJS is much less common than Gilbert's.

It is due to a defect in the canalicular multispecific organic anion transporter (cMOAT) protein. This causes defective hepatic bilirubin **excretion**.

**Unconjugated** bilirubin (= **indirect**): water-**insoluble**, so **not** pass to urine (normal colour).

**Conjugated** bilirubin (= **Direct**): it is **water-soluble** so **pass to urine (dark)**.

### Hepatosplenomegaly

#### Causes of hepatosplenomegaly:

- 1) Chronic liver disease with portal hypertension. E.g. Hepatitis, alcohol.
- 2) Infections: glandular fever, malaria, hepatitis
- 3) Lymphoproliferative disorders
- 4) Myeloproliferative disorders e.g. CML
- 5) Amyloidosis

NB: The latter stages of cirrhosis are associated with a small liver.

NB: Infective endocarditis normally causes an isolated splenomegaly. Theoretically severe infective endocarditis may cause right heart failure and hence hepatomegaly but this would be unusual.

### Liver biopsy

Contraindications to percutaneous liver biopsy:

- 1) Deranged clotting (e.g. INR > 1.4)
- 2) Low platelets (e.g.  $\leq 60 \times 10^9/l$ )
- 3) Anaemia
- 4) Bile duct obstruction / dilatation
- 5) Hydatid cyst
- 6) Haemoangioma
- 7) Ascites
- 8) Uncooperative patient: as sudden movement can result in laceration to the liver.

Anti-platelet medication should be stopped for at least 7 days prior to biopsy.

If the INR is  $>1.4$ , fresh frozen plasma (FFP) may be administered and liver biopsy then carried out if the INR is less than 1.4.



Significant volume ascites is a contraindication to percutaneous liver biopsy but a transjugular biopsy can be performed as an alternative.

**NB:** With modern techniques such as ERCP and MRCP the risks of liver biopsy when there is extra-hepatic biliary obstruction are rarely justified.

### Budd-Chiari Syndrome

It is obstruction of venous outflow from the liver caused by **hepatic vein** occlusion.

The cause is unknown in 1/3 of cases.

Causes:

- **Thrombosis:** usually in association with a hypercoagulable state such as primary polycythaemia, thrombophilia and leukaemia.
- **Malignancy:** hepatocellular, renal and adrenal.
- Radiotherapy
- **Oral contraceptive pills.**
- Trauma
- Congenital venous webs.

It can present either acutely or chronically.

In the **acute** form there is, **abdominal pain**, nausea, vomiting, **ascites**, **tender hepatomegaly**, **jaundice** even **fulminant hepatic failure**.

Signs of **portal hypertension** are present and patients may develop acute variceal haemorrhage as a complication.

<b>Budd-Chiari S: Triad: Abdomen pain+ tender Hepatomegaly + Ascites</b>
--

The chronic form presents more insidiously with signs of cirrhosis and portal hypertension.

<b>Three</b> year survival in patients with chronic Budd-Chiari syndrome is <b><u>50%</u></b> .
---

Investigations:

- **Colour Doppler US for hepatic vasculature.**
- US, CT or MRI Abdomen: **enlarged caudate lobe: is a characteristic sign** but is seen in **only 50%** of cases.
- Ascitic tap usually demonstrates a **high SAAG (>11g/L)**.

Management:

- TTT of the underlying cause.
- Portocaval shunts and TIPSS
- Streptokinase and subsequent anticoagulation may be attempted if the thrombus is known to be of a recent onset.
- Liver transplantation.

**EX:** A 40-year-old woman with abdominal pain and increasing abdominal girth. Her symptoms have been progressing over several months. There is no history of jaundice. She has a **past history of pulmonary embolism** for which she was treated with warfarin 5 years ago.

O/E, she has **mildly jaundiced sclerae**. She is alert and orientated, there is no encephalopathy. Abdominal examination reveals **ascites** and **hepatosplenomegaly**.

You arrange an abdominal ultrasound scan with Dopplers which demonstrates and confirms hepatosplenomegaly and moderate ascites.

What is the most likely underlying diagnosis >>> **Budd-Chiari syndrome**.

### Ascites

<b>Exudate ascites</b> <b>(Protein content &gt; 30 gm/L)</b> <b>(High albumin gradient)</b> <b>(Non-portal hypertensive causes)</b> <b>(SAAG &lt; 11 gm/L)</b>	<b>Transudate ascites</b> <b>(Protein content &lt; 30 gm/L)</b> <b>(Low albumin gradient)</b> <b>(Portal hypertensive causes)</b> <b>(SAAG &gt; 11 gm/L)</b>
<ul style="list-style-type: none"> <li>➤ Hepatic/peritoneal <b>malignancy</b>.</li> <li>➤ TB <b>peritonitis</b>.</li> <li>➤ Nephrotic syndrome.</li> <li>➤ Pancreatitis.</li> <li>➤ Pancreatic duct leak with biliary peritonitis.</li> <li>➤ Protein losing enteropathy.</li> </ul>	<ul style="list-style-type: none"> <li>➤ <b>Liver cirrhosis</b> and <b>portal HTN</b></li> <li>➤ Portal vein obstruction/thrombosis.</li> <li>➤ Budd-Chiari Syndrome.</li> <li>➤ SBP.</li> <li>➤ <b>CHF</b>.</li> <li>➤ Myxoedema.</li> </ul>

### SAAG (Serum-Ascites Albumin Gradient) 11 gm/L:

- SAAG is considered the **most sensitive and specific method** of categorising ascites.
- It is calculated by subtracting the ascetic fluid albumin value from the serum albumin value.
- It correlates **directly** with **portal hypertension**.
- The accuracy of the SAAG results is approximately 97% in classifying ascites.

**NB:** Increase ascites **amylase** level >>> Pancreatitis ascites.

**NB:** The ascetic total **WBCs** > 500/ MicroL or **neutrophil** count > 250/ MicroL is diagnostic of bacterial peritonitis.

**NB: Abdominal Tuberculosis** should always be suspected in the severely malnourished patient and is difficult to diagnose, SAAG < 11 gm/L, high ascetic WBC mainly lymphocytes, should do >>> **Laparoscopy** and **peritoneal biopsy** is diagnostic in 95% of cases.

### **Hereditary Haemochromatosis (HHC)**

Haemochromatosis is an **autosomal recessive** disorder (AR) of iron absorption and metabolism resulting in iron accumulation.

It is caused by inheritance of mutations in the **C282Y HFE** gene on both copies of chromosome 6.

**Two** mutations of the **HFE gene (C282Y and H63D)** account for **over 90%** of cases in Europeans.

The disease is also associated with HLA-A3 and HLA-B14.

It is caused by dysregulated iron homeostasis due to **inappropriate increased iron absorption** in the duodenum and proximal small intestine with **subsequent iron deposition in cells** of the liver, heart, pancreas and pituitary gland resulting in tissue damage and organ failure.

It is relatively common in **Caucasians**, usually presents in **men over the age of 40 years**, and is much less common in women, presumably due to continuous menstrual blood loss.

The combination of **pituitary dysfunction, arthralgia/arthritis, DM, hepatomegaly (cirrhosis)** with **normal LFTs** and **cardiomyopathy** >>>> Haemochromatosis.

The British Committee for Standards in Haematology (BCSH) published guidelines for the investigation and management of haemochromatosis in 2000.

There is continued debate about the best investigation to **screen** for haemochromatosis. The 2000 BCSH guidelines suggest:

- **General population:** transferrin saturation is considered the most useful marker. Ferritin should also be measured but is not usually abnormal in the early stages of iron accumulation
- **Testing family members:** genetic testing for HFE mutation.

These guidelines may change as HFE gene analysis become less expensive

**Screening for haemochromatosis:**

- **General population:** Transferrin saturation > ferritin
- **Family members:** HFE genetic testing

**N.B:**

- BCSH guidelines recommend measuring the **transferrin saturation** first as this is the most specific and sensitive test for iron accumulation.
- They also recommend that serum ferritin is measured but this marker is not as useful as it is usually not abnormal in the early stages of iron accumulation, also it is an acute phase reactant and it may be raised in alcoholic liver disease.
- There are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene.

**Presenting features:**

It is due to iron deposition in **(6)**:

**Anterior pituitary, skin, heart, joints, pancreas (DM) and liver.**

- 1) Often asymptomatic in early disease and initial symptoms often non-specific e.g. **lethargy** and **loss of libido with erectile dysfunction**.
- 2) **Joints: Arthralgia/arthritis often of the hands** esp. the **2<sup>nd</sup> and 3<sup>rd</sup> metacarpo-phalangeal joints (MPJ)**, **wrist, knee** with **chondrocalcinosis** and **Pseudogout**.
- 3) **Bronze skin pigmentation** (Skin pigmentation rather than a rash).
- 4) **DM (MODY): only 17%** of non-cirrhotic patients will have manifest diabetes at time of diagnosis.
- 5) **Liver:** stigmata of chronic liver disease, hepatomegaly, cirrhosis, spider naevi, sparse pubic hair, hepatocellular deposition, HCC.
- 6) **Cardiac** failure or dysrhythmia (secondary to **DCM**).
- 7) Hypogonadism (secondary to cirrhosis and **pituitary** dysfunction-**Hypogonadotropic hypogonadism**).

Reversible complications	Irreversible complications
<ul style="list-style-type: none"> <li>• Cardiomyopathy القلب</li> <li>• Skin pigmentation الجلد</li> </ul>	<ul style="list-style-type: none"> <li>• Arthropathy</li> <li>• DM</li> <li>• Liver cirrhosis</li> <li>• Hypogonadotrophic hypogonadism</li> </ul>

**Both** males and females are affected equally, but females are often 'protected' from the clinical features by menstrual blood loss.

**Early** diagnosis and treatment is critical in haemochromatosis as survival and morbidity are improved if phlebotomy is initiated prior to the development of cirrhosis.

If cirrhosis develops, there is an increased risk of HCC.

**Transferrin saturation** is suggested as the initial screening test: a level of **more than 45%** warrants further investigation (**less than 45% usually excludes the diagnosis**).

**Genetic screening** is then performed. If the usual **C282Y HFE** mutation is found this makes the diagnosis.

If the C282Y HFE mutation is not present **other genotypes** should be looked for and if present **a liver biopsy** is indicated.

In the event of rarer mutations confirmation with liver biopsy may be required.

**Ferritin** is measured to help guide further investigation and treatment: **if more than 1000 >>> a liver biopsy** should be performed and treatment initiated.

If the ferritin is within normal range and the liver function tests are normal patients can be followed closely.

**High serum ferritin and transferrin saturation** in the **absence** of biochemical or ultrasonographic evidence of cirrhosis points to a diagnosis of haemochromatosis.

Pt with **DM** and **impotence** with ↑ **ferritin >>> a suspected diagnosis** of haemochromatosis >>> the next most appropriate investigation is >>> **Transferrin saturation %** >>> **if elevated above 45% >>> genotyping** (homozygosity for **C282y HFE mutations** would next be considered and would be expected to clinch the diagnosis.

#### Diagnostic tests:

- 1) **High Transferrin saturation.**
- 2) **Molecular genetic testing** for the **C282Y HEF** and **H63D** mutations

- 3) Liver biopsy: Perl's stain.
- 4) Screening for the first degree relatives.

**Liver biopsy** remains the **gold standard** for the diagnosis of haemochromatosis as it quantifies iron deposition and also stages the amount of fibrosis.

**Typical iron study profile in patient with haemochromatosis:**

- 1) ↑ Iron.
- 2) Low TIBC.
- 3) ↑ Ferritin (e.g. > 500 ug/l) and
- 4) ↑ Transferrin saturation > **55%** in men or > **50%** in women.

**Treatment:**

- 1) **Repeated venesection**: is the cheapest and most effective treatment.
- 2) **Iron chelation with desferrioxamine**: it is not used except in rare situations when venesection is impracticable.
- 3) **Liver transplantation**.

The goal of therapy is to remove excess body iron stores which is commonly done via **phlebotomy**. Initially this is **weekly** or **twice weekly** (if tolerated) venesections of 500 cm<sup>3</sup> until the serum ferritin is less than 50 ng/mL. Transferrin saturation should also be reduced to less than 50% if possible.

Monitoring adequacy of venesection: BSCH recommends:

**Transferrin saturation** should be kept below **50%** and the serum **ferritin** concentration below **50 ug/l**.

After these goals are reached maintenance therapy is typically required three to four times per year.

When iron overload and anaemia are present concomitantly **chelation with desferrioxamine** may be required.

Patients should be told to avoid vitamin C supplementation as this can enhance iron toxicity.

End stage liver disease, portal hypertension and hepatocellular carcinoma (which is increased up to 200-fold) may necessitate liver transplantation.

**N.B:** Joint x-rays characteristically show **chondrocalcinosis**.

**Wilson's disease (Hepato-lenticular degeneration)**

Wilson's disease is a rare **autosomal recessive (AR)** disorder of **copper metabolism** characterised by **failure of copper excretion in the bile** and so excessive copper deposition in the tissues especially in the **liver, eye** and **brain** and impaired incorporation of copper into caeruloplasmin.

Metabolic abnormalities include increased copper absorption from the small intestine and decreased hepatic copper excretion.

Wilson's disease is caused by a defect in the **ATP7B gene** located on **chromosome 13**.

**The average prevalence is 30/million.**

The onset of symptoms is usually between 5 - 30 years.

Children usually present with liver disease whereas the first sign of disease, while in young adults is often neurological disease.

Features result from excessive copper deposition in the tissues, especially the brain, liver and cornea:

- 1) **Liver:** asymptomatic hepatomegaly, hepatitis, cirrhosis.
- 2) **Neurological:** Extrapyramidal signs, basal ganglia degeneration, speech and behavioural problems are often the first manifestations. Also: asterixis, chorea, dementia, depression, neurotic behaviour.
- 3) **Eye:** Kayser-Fleischer (KF) rings (copper deposition in Descemet's membrane of the cornea) by **slit-lamp examination**: it is the **most rapid diagnostic pathognomonic sign** (present in **60%** of cases) (greenish gold discoloration within the limbus of cornea), although rarely it may be absent.
- 4) **Kidney:** Renal tubular acidosis type II (esp. Fanconi syndrome).
- 5) Others: Haemolysis, Blue nails, low serum phosphate and uric acid.

**Wilson's disease** should be suspected in **any young adult** with **neuropsychiatric symptoms** and a **family history of liver disease**.

Combination of **Parkinsonism** and **chronic liver disease** in a **young** person is highly suggestive of **Wilson's** disease.

**Diagnosis:**

- 1) **Increased 24hr urinary copper excretion:** greater than 3  $\mu\text{mol}$  (100-1000 mg/24 hours).
- 2) **Reduced serum caeruloplasmin:** < 200 mg/L: not specific.
- 3) **Reduced serum copper:** < 11  $\mu\text{mol/L}$
- 4) Liver biopsy will aid the diagnosis.
- 5) MRI brain commonly shows increased density in the basal ganglia.

Once a diagnosis of Wilson's disease is made, **screening** of **first** degree relatives (with **genetic** testing) should be done.

#### Management:

- 1) **Penicillamine** (chelates copper) (**0.75-1.5 gm/day**): it has been the traditional first-line treatment. It leads to urinary copper excretion.
- 2) **Trientine HCL 50 mg TID** is an alternative chelating agent which may become first-line treatment in the future as it is less toxic.
- 3) **Zinc 50 mg oral TID**: it inhibits intestinal absorption of copper.
- 4) Tetrathiomolybdate is a newer agent that is currently under investigation.

#### **Drug-induced liver disease**

Drug-induced liver disease is generally divided into hepatocellular, cholestatic or mixed. There is however considerable overlap, with some drugs causing a range of changes to the liver.

Elevation of the ALP in excess of hepatic transaminases (ALT & AST) indicates a cholestatic pattern of injury/jaundice.

The following drugs tend to cause a **hepatocellular** picture:

- Paracetamol
- Sodium valproate, phenytoin
- MAOIs
- Halothane
- Anti-tuberculosis: isoniazid, rifampicin, pyrazinamide
- Statins
- Alcohol
- Amiodarone
- Methyldopa

The following drugs tend to cause **cholestasis (+/- hepatitis)**:

- Oral contraceptive pill
- Antibiotics: flucloxacillin, co-amoxiclav, ciprofloxacin, erythromycin\*, nitrofurantoin
- Anabolic steroids, testosterone
- Phenothiazines: chlorpromazine, prochlorperazine
- Sulphonylureas
- Fibrates
- Rare reported causes: nifedipine



Liver **cirrhosis**:

- Methotrexate
- Methyldopa
- Amiodarone

\*risk may be reduced with erythromycin stearate

Flucloxacillin + co-amoxiclav are well recognised causes of cholestasis

Some drugs may produce jaundice by inducing haemolysis (for example, dapsone).

Elevation of transaminases to this extent (more than 100 times the upper limit of normal, about **10,000**) generally occurs in **only 2 conditions** - **ischemic hepatitis** and **paracetamol overdose**.

The near-normal INR in the presence of significant hepatocellular damage also counts against a diagnosis of paracetamol overdose.

**Halothane** induced hepatitis typically occurs **5 to 7 days after** exposure.

Statin-induced hepatitis is unlikely to have developed acutely (with normal LFTs on admission).

### Alkaline phosphatase

Causes of raised alkaline phosphatase (ALP):

- Liver: cholestasis, hepatitis, fatty liver, neoplasia
- Paget's
- Osteomalacia
- Bone metastases
- Hyperparathyroidism
- Renal failure
- Physiological: pregnancy, growing children, healing fractures

The table below splits the causes according to the calcium level:

Raised ALP and raised calcium	Raised ALP and low calcium
<ul style="list-style-type: none"><li>• Bone metastases</li><li>• Hyperparathyroidism</li></ul>	<ul style="list-style-type: none"><li>• Osteomalacia</li><li>• Renal failure</li></ul>

**NB:** Alkaline phosphatase is significantly elevated in pregnancy. This would also explain the borderline anaemia that may be associated with pregnancy.

### Acute pancreatitis: causes

The vast majority of cases in the UK are caused by gallstones and alcohol.

Popular mnemonic is **GET SMASHED**:

- **G**allstones
- **E**thanol
- **T**rauma
- **S**teroids
- **M**umps (other viruses include Coxsackie B)
- **A**utoimmune (e.g. polyarteritis nodosa), **A**scaris infection
- **S**corpion venom
- Hypertriglyceridaemia, Hyperchylomicronaemia, Hypercalcaemia, Hypothermia
- **ERCP**
- **D**rugs (Azathioprine, Mesalazine, Sulphasalazine, 5 ASA, Didanosine, Bendroflumethiazide, Furosemide, GLP-1 agonists, Pentamidine, Steroids, Oestrogen, Octreotide, Sodium valproate, and methyldopa).
- **P**ost-burn pancreatitis.

### N.B:

- Pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine.
- Sodium valproate induced pancreatitis is more common in young adults and tends to occur within the first few months of treatment. Asymptomatic elevation of the amylase level is seen in up to 10% of patients.
- CRP is now a widely used marker of severity in acute pancreatitis. Other methods which have to correlate with prognosis include the Ranson criteria and APACHE II score (Acute Physiology and Chronic Health Evaluation).
- Post-ERCP pancreatitis (The acute pancreatitis following ERCP) should be treated with IV fluids and analgesia. Quinolones have not been shown to be beneficial in acute pancreatitis.
- Pancreatitis occurs in around 1 in 2,000 pregnancies. Most cases of pancreatitis in pregnancy are gallstone related.

- Hyperchylomicronaemia may be caused by hereditary lipoprotein lipase (LPL) deficiency and apolipoprotein CII (Apo CII) deficiency. It predisposes to recurrent attacks of acute pancreatitis.
- The **mortality** associated with severe acute pancreatitis is approximately **20%**.

There are a number of criteria used in the Ranson's scoring system which reflect **prognosis** associated with **acute pancreatitis**.

Ranson's criteria on admission and at 48 hrs of admission that signify a worse prognosis include:

### Criteria present at 0 hours:

- 1) **Age >55** years old - 1 point
- 2) **WBC >16**  $\times 10^9$  - 1 point
- 3) **Glucose (FBS) >11.1** mmol/L - 1 point
- 4) **LDH >350** U/L - 1 point
- 5) **AST >250** U/L - 1 point

### Criteria present at 48 hours:

- 1) **Haematocrit fall** of  $\geq 10\%$  - 1 point
- 2) **Urea > 16** mmol/L or **BUN** rise of **1.8** mmol/L or more despite fluids - 1 point
- 3) Serum **Calcium < 2** mmol/L - 1 point
- 4) Serum **Albumin < 32** g/L
- 5) **PO2 <60** mmHg (< 8 kPa) - 1 point
- 6) **Base deficit >4** meq/L - 1 point
- 7) **Fluid sequestration > 6000 mL** - 1 point

If $\geq 3$ of these criteria within the 1st 48 hours >> <b>severe</b> pancreatitis >> <b>ICU</b> .
---

**TTT** of acute pancreatitis: Oxygen therapy and **fluid resuscitation** have been shown in RCT to reduce the chances of prolonged organ failure and so decrease the mortality. The use of antibiotics is debatable.

**Complications:** Pancreatic pseudocyst: cannot be diagnosed **until more than 6 weeks** after the acute attack and may present with abdominal **pain** or a **mass**, **fever** and **persistently raised amylase**.

### **Chronic pancreatitis**

Chronic pancreatitis is an inflammatory condition which can ultimately affect **both** the **exocrine** and **endocrine** functions of the pancreas.

Approximately 60% of patients survive 2 years.

### Causes:

- **Alcohol.**
- **Cystic fibrosis.**
- Haemochromatosis.
- Sclerosing cholangitis.
- Unknown.

Around **80%** of cases are due to **alcohol** excess with up to 20% of cases being unexplained.

The most common cause in **adult** is **alcohol**, and in **children** is **Cystic fibrosis**.

### Features:

- 1) **Pain** is typically worse 15 to 30 minutes following a meal
- 2) **Steatorrhea**: symptoms of pancreatic insufficiency usually develop between 5 and 25 years after the onset of pain
- 3) **Diabetes mellitus** develops in the majority of patients. It typically occurs more than 20 years after symptom begin

### Investigation:

- Abdominal x-ray shows pancreatic calcification in 30% of cases
- CT is more sensitive at detecting pancreatic calcification. Sensitivity is 80%, specificity is 85%.
- Functional tests:
  - Faecal elastase may be used to assess exocrine function if imaging inconclusive.
  - Secretin stimulation test.
- MRCP/ERCP to rule out mass lesion if with significant weight loss.

Faecal elastase is for test the **exocrine** pancreatic insufficiency.

It is non-invasive and can be performed **on a single stool sample**.

**Low** levels of faecal elastase are **indicative** of pancreatic exocrine deficiency and predictive of the response to supplementation.

(N= more than 200 Mcg/ gm faeces).

Even the secretin stimulation test, which is the **most sensitive** method of assessing pancreatic exocrine function, it is **invasive** and therefore not a preferred investigation. Also it is probably abnormal only when more than 60% of exocrine function has been lost.

**Secretin stimulation test:**

It involves positioning a tube inside the duodenum and collecting pancreatic secretions stimulated by IV secretin alone or with either cholecystokinin.

Duodenal contents are collected for volume determination, HCO<sub>3</sub> concentration and enzyme concentration.

**Normal volume is > 2 ml/kg and Normal HCO<sub>3</sub> is > 80 mEq/l**

If **normal** volume (> 2ml/kg) + **low** HCO<sub>3</sub> (< 80 mEq/l) >>> suggests **chronic pancreatitis**.

If **low** volume (< 2ml/kg) + **normal** HCO<sub>3</sub> (> 80 mEq/l) + normal enzyme levels >>> **pancreatic duct obstruction** perhaps secondary to tumour and should prompt ERCP.

**Chronic pancreatitis >>>> with LOW HCO<sub>3</sub>**

**Pancreatic duct obstruction >>>> with LOW VOLUME**

**NB: Faecal fat excretion is high (> 30 gm/3 days) (steatorrhoea) indicating pancreatic enzyme insufficiency.**

**Management:**

- Stop alcohol
- Pancreatic enzyme supplements
- Analgesia
- Antioxidants: limited evidence base - one study suggests benefit in early disease.

**Pancreatic cancer**

**Features:**

- Classically **painless obstructive jaundice**.
- However, patients typically present in a **non-specific way** with anorexia, nausea, malaise, mild epigastric pain, recent onset DM and significant weight loss which is a characteristic feature.
- Pancreatic cancer is the **3<sup>rd</sup>** most common malignancy affecting the GIT, but it is a **difficult disease to diagnose in its early stages** and therefore most patients present at an advanced and incurable stage.
- The most useful tumour marker for pancreatic cancer is **CA 19-9**, of which the sensitivity and specificity for pancreatic carcinoma are 80% and 90% respectively.

- CA 19-9 does not distinguish between cholangiocarcinoma, pancreatic or gastric carcinoma and may also be raised in patients with severe liver injury due to any other cause.
- The accuracy of using CA 19-9 to identify patients with small surgically resectable tumours is limited.

The history of **post-prandial abdominal pain** accompanied with **weight loss** and **intermittent diarrhoea** is consistent with **pancreatic involvement** >>>? **Pancreatic adenocarcinoma**

#### Associations:

- Smoking
- Diabetes
- Chronic pancreatitis
- Hereditary pancreatitis
- Hereditary non-polyposis colorectal carcinoma
- Multiple endocrine neoplasia (MEN)
- Peutz-Jeghers syndrome (PJS)
- BRCA2
- Dysplastic naevus syndrome

#### Management:

- Less than 20% are suitable for surgery at diagnosis
- Radio and chemotherapy are ineffective.

#### **Sphincter of Oddi dysmotility (SOD)**

SOD can cause backup of bile and pancreatic juices which can result in biliary colic.

More prolonged obstruction may result in bile leaking back into the blood stream, which can cause **transient abnormal liver biochemistry**.

SOD most commonly occurs in **young females** especially those who have **previously undergone cholecystectomy**.

Usually **normal** abdominal **US**, **OGD** and **MRCP**.

By **ERCP**: delayed drainage of contrast.

**SOD manometry** can confirm the diagnosis: high resting pressure with marked phasic contractions and often some retrograde peristalsis.

TTT: **Endoscopic sphincterotomy** or **balloon sphincteroplasty** by ERCP.

**Coeliac disease**

The prevalence of coeliac disease is **1% in western societies** and is thus **one of the commonest immune-mediated diseases**.

The **prevalence** of coeliac disease in **Europe** varies widely and is in the region of between **1:100** and **1:300** and as much as **1:30** in the **west of Ireland**. It is more common in the Celtic population.

Coeliac disease is caused by **sensitivity** to the protein **gluten**.

The condition is caused by an **immunological reaction** to the **gliadin**, a protein fraction of **gluten** found in **wheat**, which provokes an inflammatory response and results in partial or total **villous atrophy** in the **proximal small bowel** (which resolves with a gluten-free diet).

It can present at **any age** (**peaks** occur in **babies** and in the **third** decade). Women are slightly more commonly affected.

Repeated exposure leads to **villous atrophy** which in turn causes **malabsorption**.

Conditions associated with coeliac disease include **dermatitis herpetiformis** (a vesicular, pruritic skin eruption) and autoimmune disorders (type 1 DM and autoimmune hepatitis).

It is strongly associated with **HLA-DQ2**, **HLA-DQ8** (**95%** of patients) and HLA-B8 (80%) as well as HLA-DR3 and HLA-DR7. and also from the specific immune response to the alpha-gliadin component of gluten.

The action of tissue transglutaminase (TTG) on alpha-gliadin generates epitopes to **CD4+ T-lymphocytes**, which provoke an inflammatory response in the intestinal wall.

In untreated individuals, alpha-gliadin specific **CD4+** T cells can be found producing interferon-gamma in the intestinal wall.

Coeliac disease results from **small bowel inflammation and atrophy** due to **T cell mediated hypersensitivity reaction** to the alpha-gliadin component of gluten. Other T-cell mediated autoimmune disorders may be associated with coeliac disease: **Type I DM**, **dermatitis herpetiformis** and **Hashimoto's thyroiditis**.

In 2009 NICE issued guidelines on the investigation of coeliac disease. They suggest that the following patients should be screened for coeliac disease:

Signs and symptoms	Conditions
<ul style="list-style-type: none"> <li>• <b>Unexplained iron-deficiency anaemia</b>, or other unspecified anaemia is the <b>most common</b> presentation of coeliac disease with positive <b>FOB in 50%</b> of cases.</li> <li>• <b>Chronic diarrhoea/ steatorrhoea (ONLY in 30% of cases)</b> of coeliac).</li> <li>• Persistent or unexplained gastrointestinal symptoms including nausea and vomiting.</li> <li>• <u>Prolonged fatigue</u> ('tired all the time').</li> <li>• Recurrent abdominal pain, cramping or distension.</li> <li>• Sudden or unexpected weight loss.</li> <li>• Failure to thrive or faltering growth (in children).</li> </ul>	<ul style="list-style-type: none"> <li>• Autoimmune <b>thyroid</b> disease (<b>Hashimoto's</b>).</li> <li>• <b>Type 1 DM</b>.</li> <li>• <b>Dermatitis herpetiformis</b>.</li> <li>• Irritable bowel syndrome.</li> <li>• First-degree relatives (parents, siblings or children) with coeliac disease.</li> </ul>

Symptoms of Coeliac disease are often **mild** and **non-specific** which is why the diagnosis is **missed** if there is not a high index of suspicion.

It can occur at **any age** and is usually present with **diarrhoea, weight loss, lethargy, anaemia** (Fe, B12, folic), **skin itchy rash** (dermatitis herpetiformis).

If you see a **young** patient with **nutritional deficits** (B12, folate, iron) then you should check antibodies.

In **women aged less than 50 years** who **menstruate regularly**, menstrual blood loss is a common cause of IDA, although **coeliac disease** with minimal symptoms is recommended as initial step screening.

Patients with coeliac disease present with diarrhoea, **steatorrhoea**, oral ulcers, weight loss, malaise and abdominal pain. Nutritional deficiencies can result in neurological symptoms (ataxia, weakness, and paraesthesia) and amenorrhoea. Folate, B12 or iron deficiency **anaemia** can be present as can osteomalacia and (**abnormal liver function** tests in 10-15% of cases). Some patients have **dermatitis herpetiformis** (an itchy rash mainly affecting the extensor aspects of the elbows).

**Young pt. with IDDM and anaemia >>? Coeliac disease >> check (TTG IgA).**



**Diagnosis:**

Coeliac disease – (TTG IgA) tissue transglutaminase antibodies **first-line** test

- Tissue transglutaminase antibodies (IgA) are recommended as the first-line serological test according to NICE (in over 90% of cases).
- This test may be invalid in the presence of selective IgA deficiency, which is much commoner in patients with coeliac disease (2.6%).

Diagnosis of coeliac disease is made by a combination of **immunology** and **jejunal biopsy**.

**NB:** Villous atrophy and immunology normally reverses on a gluten-free diet.

NICE issued guidelines on the investigation of coeliac disease in 2009. If patients are already taking a gluten-free diet they should be asked, if possible, to reintroduce gluten (i.e. the patient should eat some gluten in more than one meal every day) for at least 6 weeks before further testing.

**Immunology:**

- Tissue transglutaminase (TTG) antibodies (IgA) are first-choice, it has very high sensitivity and specificity of 100%.
- Anti-Endomyseal antibody (EMA) (IgA).
- Anti-casein antibodies are also found in some patients.
- Anti-gliadin antibody (IgA or IgG) tests are not recommended by NICE.

**Jejunal biopsy:** (Appearances may resemble severe **tropical sprue**):

- 1) **Villous** atrophy.
- 2) **Crypt** hyperplasia/hypertrophy.
- 3) Increase in intraepithelial **lymphocytes**
- 4) Lamina propria infiltration with **lymphocytes**

Rectal gluten challenge has been described but is not widely used

**Complications:**

- Anaemia: iron, folate and vitamin B12 deficiency. (Folate deficiency is more common than vitamin B12 deficiency in coeliac disease).
- Hypo-splenism: **Howell-Jolly bodies** on blood film.
- Osteomalacia ( $\downarrow$ Ca,  $\uparrow$  ALP) due to Vit D deficiency due to its malabsorption with subsequent hyperparathyroidism.
- Osteoporosis.
- **Malabsorption** , **low serum albumin** and **weight loss**

- Lactose intolerance.
- Subfertility, unfavourable pregnancy outcomes.
- Oesophageal cancer (rare).
- Enteropathy-associated T-cell lymphoma of small intestine: It is associated with increased risk of developing **small bowel lymphoma**, which thankfully only occurs in a very small portion of coeliac patients, which gives a clinical and radiological picture of **small bowel obstruction**.

Long term risks associated with coeliac disease include **oesophageal carcinoma** and **small bowel lymphoma**, particularly in patients who fail to follow the gluten free regimen.

**NB:** **Small bowel malignancies**, particularly lymphomas, are more common in those with coeliac disease and would be a potential consideration here.

Risk is increased in those not adhering to a gluten free diet (GFD) or with poor mucosal healing on a GFD. That having been said they are still very rare and many **(40-50%)** are diagnosed **simultaneously** with coeliac disease. >>> Evaluation of the small bowel with CT or MR Enterography.

**NB:** Coeliac disease may cause malabsorption of iron and folate causing anaemia with either micro- or macrocytosis. Sometimes the **MCV** may be '**normal**' due to a deficiency of **both** causing a **bimodal distribution** of red cell volumes which has an average in the normal range. If patients have additional reasons to be deficient in either folate or iron (e.g. menorrhagia in women) then that may dominate the clinical picture.

**NB:** **Howell-Jolly bodies** on blood film indicate **hyposplenism** and are consistent with a diagnosis of coeliac disease.

**NB:** Selective IgA deficiency is more common in patients with coeliac disease. It is relatively common in a Caucasian population with a frequency of around 1:1000, it is much more common in individuals with a history of atopic or autoimmune disease. For this reason IgA levels should be checked when serological tests are ordered. If the patient has selective IgA deficiency tissue transglutaminase IgG can be measured.

**NB:** Patients normally need to be following a gluten-free diet (GFD) for at least 6 months before the serology becomes negatives.

#### **Management:**

The management of coeliac disease involves a gluten-free diet (GFD).

Gluten containing cereals include☹

- Wheat: bread, pasta, pastry

- Barley\*: beer
- Rye
- Oats\*\*

Some notable foods which are gluten-free include☺

- Rice
- Potatoes
- Corn (maize)

Folate, iron and calcium supplements may be required.

\*whisky is made using malted barley. Proteins such as gluten are however removed during the distillation process making it safe to drink for patients with coeliac disease.

\*\*some patients with coeliac disease appear able to tolerate oats.

**EX:** Male patient 44 years old, 10-months history of pain in low back, hips, ankles and feet, tiredness, loss of weight despite eating reasonable meals, pale, anaemia Hb 7, low MCV, positive FOB, low albumin, low calcium, high PTH, prolonged INR >>> **Coeliac disease** with **malabsorption** of iron (IDA), Ca, Vit D (osteomalacia) and Vit K (impaired clotting), associated autoimmune hypothyroidism.

**EX:** Female pt. 16 years old with loose motions for 8 weeks, loss of weight, lethargy, anaemia Hb 9 gm%, itchy rash over both elbows >>> **Coeliac** disease associated with **dermatitis herpetiformis**.

**EX:** Male pt. 60 years old known to have coeliac disease and presented with a clinical and radiological picture of **small bowel obstruction** >>> **small bowel lymphoma** (malignant transformation of coeliac to small bowel lymphoma).

**EX:** Male pt. 40 years old known to have **Coeliac disease**, he has significant **weight loss** and **night fever** >>> **Enteropathy-associated T-cell lymphoma of small intestine**.

Poor compliance to coeliac diet may increase the propensity for malignancy.

**EX:** Female pt. 15 years old has **primary amenorrhoea**, **loss of weight**, low BMI, **occasional diarrhoea**, **anaemia Hb is 10 gm%**, low FSH, low LH, and low Oestradiol but with normal testosterone, normal TSH, **low albumin** >>> **Coeliac disease not** anorexia nervosa.

### Tropical sprue

It occurs in **tropical area**, predominantly **Central America** and **South-Eastern-Asia** (e.g. **Thailand trip**).

It is thought that an initial GI infection results in small bowel stasis, opportunistic colonisation by organisms such as **coliforms**, and then a degree of **villous atrophy** leading to **malabsorption** and B12, folate deficiency.

**Jejunal biopsy**: villous atrophy, increased crypts and mononuclear cell infiltrates, lipid accumulation below the basement membrane and **coliforms** bacteria may be isolated.

Treatment:

- **Prolonged course of Tetracycline** for 3-6 months (**avoid pregnancy** while taking the antibiotics).
- Vitamin replacement.

### Inflammatory bowel disease (IBD): key differences

The 2 main types of IBD are Crohn's disease (CD) and Ulcerative colitis (UC). They have many similarities in terms of presenting symptoms, investigation findings and management options. There is however some key differences which are highlighted in table below:

	Crohn's disease (CD)	Ulcerative colitis (UC)
<b>Features</b>	<ul style="list-style-type: none"> <li>• Diarrhoea usually non-bloody.</li> <li>• <u>Weight loss</u> more prominent.</li> <li>• <u>Upper</u> GI symptoms, <u>mouth ulcers</u>.</li> <li>• <u>Perianal</u> disease.</li> <li>• Abdominal mass palpable in the <u>right iliac fossa</u>.</li> </ul>	<ul style="list-style-type: none"> <li>• <u>Bloody</u> diarrhoea more common.</li> <li>• <u>Tenesmus</u>.</li> <li>• Abdominal pain in the <u>left lower</u> quadrant.</li> </ul>
<b>Extra-intestinal</b>	<p><u>Gallstones</u> are more common secondary to reduced bile acid reabsorption.</p> <p><u>Oxalate renal stones</u>.</p>	<p><u>Primary sclerosing cholangitis (PSC)</u> more common</p>

<b>Complications</b>	Obstruction, <u>fistula</u> , <u>anal tags</u> , colorectal cancer.	Risk of <u>colorectal cancer</u> <u>high</u> in UC than CD.
<b>Pathology</b>	Lesions may be seen <u>anywhere</u> from the mouth to anus.  <u>Skip</u> lesions may be present.	Inflammation always starts at <u>rectum</u> and <u>never</u> spreads beyond ileocaecal valve.  <u>Continuous</u> disease.
<b>Histology</b>	Inflammation in <u>all</u> layers from mucosa to serosa <ul style="list-style-type: none"> <li>• <u>↑ Goblet cells.</u></li> <li>• <u>Granulomas.</u></li> </ul>	No inflammation beyond submucosa (unless fulminant disease) - inflammatory cell infiltrate in lamina propria <ul style="list-style-type: none"> <li>• Neutrophils migrate through the walls of glands to form <u>crypt abscesses.</u></li> <li>• Depletion of goblet cells and mucin from gland epithelium.</li> <li>• Granulomas are infrequent.</li> </ul>
<b>Endoscopy</b>	<ul style="list-style-type: none"> <li>• <u>Deep ulcers.</u></li> <li>• <u>Skip lesions.</u></li> <li>• <u>'Cobble-stone' appearance.</u></li> </ul>	Widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ( <u>'pseudopolyps'</u> )
<b>Radiology</b>	Small bowel enema <ul style="list-style-type: none"> <li>• <u>High sensitivity</u> and <u>specificity</u> for examination of the terminal ileum.</li> <li>• <u>Strictures: 'Kantor's string sign'.</u></li> <li>• <u>Proximal bowel dilation.</u></li> <li>• <u>'Rose thorn' ulcers.</u></li> <li>• <u>Fistulae</u> (e.g. colovesical)</li> </ul>	Barium enema <ul style="list-style-type: none"> <li>• <u>Loss of haustrations</u></li> <li>• Superficial ulceration, 'pseudopolyps'</li> <li>• Long standing disease: colon is narrow and short -'<u>drainpipe colon</u>'</li> </ul>

\*Impaired bile acid reabsorption increases the loss calcium in the bile. Calcium normally binds oxalate.

**NB:** Pseudopolyps are seen in **both** ulcerative colitis and Crohn's disease.

**NB:** Causes of GI fistulae: Crohn's, diverticulitis and colorectal tumours.

**NB:** Diagnosis of IBD is mainly based on **clinical history, inflammatory markers, and colonoscopy & histology results.**

In around 10% of patients, it is impossible to distinguish CD from UC and this is termed an **indeterminate colitis**.

**Serological markers** may have a greater role in the future, the presence of **ASCA** (Anti-Saccharomyces Cerevisiae Antibodies) favours **CD** while **UC** is strongly associated with **pANCA**.

In a study where IBD patients are compared with control, **a positive ASCA and a negative pANCA** serology had a **50% sensitivity** and **96% positive predictive value for Crohn's disease**.

### Crohn's disease (CD): management

Crohn's disease is a form of inflammatory bowel disease.

It commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus.

NICE published guidelines on the management of Crohn's disease in 2012.

#### **General points:**

- Patients should be strongly advised to stop **smoking**.
- Some studies suggest an increased risk of relapse secondary to **NSAIDs** and the **combined OCP** but the evidence is patchy.

#### **Pathology of Crohn's:**

- Inflammation occurs in all layers, down to the serosa. This predisposes to strictures, fistulas and adhesions.
- Oedema of mucosa and submucosa, combined with deep fissured ulcers ('rose-thorn') leads to a 'cobblestone' pattern.
- Lymphoid aggregates.
- Non-caseating granulomas.

**Inducing remission:**

- **Glucocorticoids** (oral, rectal or intravenous) are generally used to **induce remission**. Budesonide is an alternative in a subgroup of patients. **There is no role of steroids in maintaining remission.**
- Azathioprine or 6-mercaptopurine may be used as an add-on medication to induce remission but is not used as monotherapy (check TPMT activity pre usage).
- Methotrexate is an alternative to azathioprine (C.I in anaemia).
- 5-ASA drugs (e.g. mesalazine) are used second-line to glucocorticoids but are not as effective as azathioprine.
- **Anti TNF therapy (Infliximab IVI):**
  - It is a useful biological therapy of Crohn's disease in refractory disease, steroids and immunosuppressant-resistant and fistulating Crohn's disease.
  - It induce a remission in 60-80% of patients.
  - If the patient responds to the initial dose, then the usual ttt regimen is a further 4 infusions at 8-weekly intervals.
  - Allergic reactions are seen in 5% of the cases.
  - It is important to exclude TB prior to starting as it can cause reactivation.
  - Patients typically continue on azathioprine or methotrexate.
- Metronidazole is often used for isolated peri-anal disease.
- **Diet in Crohn's:**
  - **Short term use of TPN** may be of benefit to allow recovery of calorie intake and improve her weight and nutritional status especially in severely debilitating patients.
  - Enteral feeding with an elemental diet may be used in addition to or instead of other measures to induce remission, particularly if there is concern regarding the side-effects of steroids (for example in young children) (debatable).
  - **Low fat medium chain triglyceride diet** is of benefit especially in patients with significant ileal resection.
  - A significant of Crohn's patients are **lactose intolerant**, so a **dairy free diet** may reduce the frequency of diarrhoea.

**Crohn's disease in pregnancy >>> Corticosteroids.**

**Maintaining remission:**

**There is no role of steroids in maintaining remission**

- 1) **Stopping smoking** is a priority.

Remember: smoking makes Crohn's worse, but may help ulcerative colitis.

- 2) **Azathioprine** or mercaptopurine is used **first**-line to maintain remission.
- 3) **Methotrexate** is used **second**-line.
- 4) **5-ASA drugs** (e.g. **mesalazine**) should be considered if a patient has had previous surgery. It is well tolerated but are **not as** effective as azathioprine.

#### **Surgery:**

- Around 80% of pts with Crohn's disease will eventually have surgery.
- Crohn's disease can **recur** following surgery.
- **Loss of the terminal ileum** frequently leads to bile salt malabsorption >>> colonic bile acid irritation leading to >> diarrhoea (**bile acid diarrhoea**) (**BAD**) with **abnormal 14C glycolate test** >>> ttt with the bile salt chelation **cholestyramine** quickly relieves the problem, also this diarrhoea may be due to **short bowel syndrome**.
- Also this ileal resection in Crohn's disease >>> reduce bile salts reabsorption >>> reduce bile salts enterohepatic circulation >>> ↑ increase the risk of **cholesterol gall bladder stones** formation.
- Extensive small bowel resection of Crohn's disease, this predisposes to the formation of **urinary calcium oxalate stones and renal colics** because of changes in the pattern of small bowel flora and electrolyte resorption >>> so ttt good hydration & dietary oxalate restriction (cocoa, peanut products, tea, coffee, wheat germ, rhubarb, beetroot, spinach, tofu and soybeans) and taking cholestyramine to bind bile salts and citrate to prevent stone formation.
- In **Crohn's** disease and after formation of **ileostomy** >>> if develop deep ulcerated areas and begin to form on the skin around the stoma, it is **Pyoderma gangrenosum** >>> TTT: **Oral prednisolone ± topical steroid**.

NB: **Lemon juice** ☺ is a natural source of citrate and its consumption by oxalate stone formers can reduce stone formation/growth.

Pt with **Crohn's** disease and underwent **extensive bowel resection** >>> **Diarrhoea** >>> it is due to **Bile acid diarrhoea** or **short bowel syndrome**.

**NB:** The **14C glycolate test** has existed since **1970s** as a way to estimate **bile acid malabsorption** and represents the best test for making the **diagnosis**.

**NB:** Assess **thiopurine methyltransferase (TPMT) activity** before offering azathioprine (Imuran) or mercaptopurine.



**NB: Diarrhea after cholecystectomy:**

-Bile acid diarrhoea (**BAD**) may affect **10%** of patients following **cholecystectomy**. Typically it is **post-prandial**; the bile, with no gall bladder to store it, is excreted directly into the gut >>> ttt: **Cholestyramine**.

- Also after OR >>> **Antibiotics** >>> **pseudomembranous colitis**.

EX: female pt. **known to have Crohn's disease**, she has worsening **diarrhoea** especially after taking a course of **Sertraline (Lustral ®)** for depression, **colonoscopy** with biopsy revealed **lymphocytic infiltration** >>> It is **lymphocytic colitis**.

**Lymphocytic colitis:**

It may occur in patients **with other forms of GIT pathology** including **Crohn's** and **Coeliac**.

**Sertraline (Lustral ®)** also appears to be associated with the development of Lymphocytic colitis.

Treatment:

- Withdrawal of the offending agent is preferable.
- Loperamide.
- Cholestyramine.
- Azathioprine (although the response to ttt may take many years).
- About 20% of patients have a spontaneous remission.

**Aminosalicylate drugs**

5-aminosalicylic acid (5-ASA) is released in the colon and is not absorbed. It acts **locally** as an anti-inflammatory. The mechanism of action is not fully understood but 5-ASA may inhibit prostaglandin synthesis.

**Sulphasalazine:**

- A combination of sulphapyridine (a sulphonamide) and 5-ASA.
- Many side-effects are due to the sulphapyridine moiety: skin rashes, oligospermia, headache, Heinz body anaemia, and agranulocytosis.
- Other side-effects are common to 5-ASA drugs (see mesalazine).

### Mesalazine:

- A delayed release form of 5-ASA
- Sulphapyridine side-effects seen in pt. on sulphasalazine are avoided.
- Mesalazine is still however associated with side-effects such as GI upset, headache, agranulocytosis, **pancreatitis**, interstitial nephritis.

### Olsalazine:

- Two molecules of 5-ASA linked by a diazo bond, which is broken by colonic bacteria.

### NB:

- Oligospermia is seen in patients taking sulphasalazine due to the sulphapyridine moiety, which is not present in mesalazine.
- Pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine.

### Ulcerative colitis (UC)

UC is a form of inflammatory bowel disease (IBD). Inflammation always starts at rectum (hence it is the most common site for UC), never spreads beyond ileocaecal valve and is continuous.

Ulcerative colitis - the **rectum** is the most common site affected

The peak incidence of ulcerative colitis is in people aged 15-25 years and in those aged 55-65 years.

The initial presentation is usually following insidious and intermittent symptoms. Features include:

- **Bloody diarrhoea**
- Urgency
- Tenesmus
- Abdominal pain, particularly in the left lower quadrant
- Extra-intestinal features (see below)

Questions regarding the 'extra-intestinal' features of inflammatory bowel disease are common:

	Common to <u>both</u> Crohn's disease (CD) and Ulcerative colitis (UC)	Notes
<b>Related to disease activity</b>	Arthritis: pauciarticular, asymmetric <b>Erythema nodosum</b> Episcleritis Osteoporosis	Arthritis is the most common extra-intestinal feature in both CD and UC Episcleritis is more common in CD
<b>Unrelated to disease activity</b>	Arthritis: polyarticular, symmetric. Uveitis <b>Pyoderma gangrenosum</b> Clubbing Primary sclerosing cholangitis	Primary sclerosing cholangitis is much more common in UC Uveitis is more common in UC

#### Pathology of UC:

- Red, raw mucosa, bleeds easily.
- Inflammation in mucosa and submucosa only.
- No inflammation beyond submucosa (unless fulminant disease).
- Widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps').
- Inflammatory cell infiltrate in lamina propria.
- Neutrophils migrate through the walls of glands to form crypt abscesses.
- Depletion of goblet cells and mucin from gland epithelium.
- Granulomas are infrequent.
- Inclusion bodies if present in biopsy this indicate **CMV** infection superimposed on UC >>> ttt: Gancyclovir.

#### Barium enema:

- Loss of haustrations
- Superficial ulceration, 'pseudopolyps'
- Long standing disease: colon is narrow and short - 'drainpipe colon'

#### Toxic megacolon:

- It is a severe colitis (**pancolitis**).
- It is defined as **dilatation of the transverse colon  $\geq 6$  cm at its widest point radiologically on abdominal x ray or CT.**

- If there is a delay in surgery toxic dilatation of the colon carries the risk of **perforation** which has a high mortality.
- It most often occurs in the context of **ulcerative** colitis, but can also occur in CD, pseudomembranous colitis, ischaemic colitis and other colitides.
- **Truelove-Witts Criteria of severe colitis:**
  - 1) **More than 6 bloody diarrhoea / day**
  - 2) **Temperature > 37.8 °C in 2 out of 4 days.**
  - 3) **HR > 90 bpm.**
  - 4) **TLC: Neutrophil count greater than  $10 \times 10^9/L$**
  - 5) **Hb < 10.5 gm/dl**
  - 6) **ESR > 30 mm/hr**
  - 7) **CRP > 30 mg/L**
  - 8) **Dilated colon  $\geq 6$  cm**
  - 9) **Other** radiological findings include loss of haustral pattern, mucosal oedema and thumb printing.
- It is an **absolute contraindication** to **Ba** enema examination because of the risk of bowel perforation.
- High mortality about 20%.
- The 2007 European Crohn's and Colitis Organisation consensus guidelines on the management of ulcerative colitis identify the following as **risk factors for the precipitation of toxic colonic dilatation:**
  - Hypokalaemia
  - Hypomagnesaemia
  - Under-treatment
  - Purgative bowel preparations for colonoscopy
  - NSAIDs
  - Opioids
  - Anti-cholinergics, and
  - Anti-diarrhoeal agents.
- TTT: in **HDU** (high dependency unit): **High dose of IV steroids + Rectal steroids + IV fluids + LMWL  $\pm$  Cyclosporine  $\pm$  Infliximab  $\pm$  surgery (colectomy).**
- Antibiotics have not been demonstrated of help.

**Severe colitis >>>> IV Fluids + IV steroids (Hydrocortisone)**

**High relapse rate for UC, with 75% of medically treated patients eventually suffering a relapse.**

**EX:** Patient known to have **ulcerative colitis** on **prednisolone** 10 mg OD and **azathioprine** 50 mg OD, then he develop **acute severe epigastric pain >>> drug-induced acute pancreatitis (azathioprine)** due to **idiosyncratic** response, it has a good prognosis.

A high index of suspicion and careful drug history are essential for diagnosis.

### **Ulcerative colitis: colorectal cancer**

#### **Overview:**

- Risk of colorectal cancer is **10-20 times** that of general population
- This increased risk is mainly related to chronic inflammation.
- Worse prognosis than patients without ulcerative colitis (partly due to delayed diagnosis)
- Lesions may be multifocal
- On **endoscopy**, **mucosal dysplasia** seen on rectal biopsy
- **Endoscopy** not CEA is a useful **screening** test of **cancer**.
- CEA is a marker of disease response to ttt, CEA may not be elevated in early stage of cancer

#### **Factors increasing risk of cancer:**

- Disease duration > 10 years
- Onset before 15 years old
- Patients with pancolitis
- Unremitting disease
- Poor compliance to treatment

Patients with **concomitant UC and PSC** are at **higher risk** for developing **cancer colon**, and it is recommended that they are screened **annually** with **colonoscopy**.

Those with **higher** risk disease, extensive colitis with moderate/severe active endoscopic/histological inflammation or stricture in past 5 years or dysplasia in past 5 years declining surgery or PSC/transplant for PSC or family history of colorectal cancer in a FDR aged < 50, **yearly** surveillance is recommended.

Those with **intermediate** risk disease, extensive colitis with moderate/severe active endoscopic/histological inflammation or post-inflammatory polyps or family history of colorectal cancer in a first degree relative aged >50, should be surveyed **3 yearly**.

Those with **low** risk disease, extensive colitis with no active endoscopic/ histological inflammation or left-sided colitis or Crohn's colitis of < 50% colon should be surveyed **5 yearly**.

The interval between subsequent colonoscopies is dependent upon the presence of risk factors and appearance at colonoscopy.

The following features make an individual **high** RISK:

- 1) Primary sclerosing cholangitis
- 2) First degree relative with colorectal cancer under the age of 50.
- 3) Dysplasia declining surgery or stricture in the last 5 years
- 4) Extensive colitis with moderate to severe inflammation.

Patients with high risk features should have **yearly** colonoscopy

Patients with IBD are considered at intermediate risk if they have any of:

- 1) Extensive mildly active inflammation
- 2) History of colorectal cancer in a first degree relative over 50 or
- 3) Post-inflammatory polyps.

These patients should have **three yearly** colonoscopy.

**Low** risk are: Individuals with extensive colitis but no active inflammation, only left-sided disease or Crohn's colitis affecting <50% of the colon are considered low risk and should be offered screening colonoscopy on a **five yearly** basis.

**NB:** Chronic inflammation is an important factor in the development of a number of cancers. An example is hepatocellular carcinoma secondary to viral hepatitis.

### Jejunal villous atrophy

Whilst coeliac disease is the classic cause of jejunal villous atrophy there are a number of other causes you need to be aware of

Causes:

- 1) Coeliac disease
- 2) Tropical sprue
- 3) Whipple's disease
- 4) Gastrointestinal lymphoma
- 5) Hypogammaglobulinaemia
- 6) Lactose intolerance (Cow's milk intolerance).

- 7) Laxative abuse
- 8) Neomycin therapy
- 9) Infectious enteritis
- 10) Giardiasis.
- 11) Norwalk agent.

### **Irritable bowel syndrome (IBS): Diagnosis & Management**

#### **Diagnosis:**

The diagnosis of IBS should be considered if the patient has had the following for **at least 6 months**:

- **Abdominal pain**, and/or
- **Bloating**, and/or
- **Change in bowel habit**

A positive diagnosis of IBS should be made if the patient has **abdominal pain relieved by defecation** or associated with **altered bowel frequency** stool form, in addition to 2 of the following 4 symptoms:

- Abdominal pain relieved by defecation
- Abdominal bloating (more common in women than men), distension, tension or hardness.
- Change in stool frequency and consistency (altered stool passage) (straining, urgency, incomplete evacuation).
- Symptoms made worse by eating.
- Passage of mucus per rectum.

Features such as lethargy, nausea, backache and bladder symptoms may also support the diagnosis.

#### **Clinical features supporting a diagnosis of IBS include:**

- A long history with a relapsing and remitting course
- Exacerbations triggered by life events
- Coexistence of anxiety and depression.
- Symptoms aggravated by eating.

#### **Red flag features should be enquired about:**

- Rectal bleeding/ Rectal mass (not due to fissures or haemorrhoids)
- Anaemia
- Abdominal mass
- Unexplained/unintentional weight loss

- Dehydration
- Steatorrhoea
- Family history of bowel or ovarian cancer
- Onset after **60** years of age.
- A **change** in bowel habit to looser and/or more frequent stools persisting for more than 6 weeks in a person aged over 60 years.
- Unintentional and unintended weight loss.
- Inflammatory markers for inflammatory bowel disease.
- Fever
- Progressive deterioration

NICE guidelines state that in the presence of a history classical for IBS (and the absence of red flag symptoms such as weight loss) the following are sufficient to exclude other causes of bowel symptoms:

Suggested primary care investigations are: **(3)**

- 1) **CBC**
- 2) **ESR/CRP**
- 3) **Coeliac disease screen (TTG-IgA)** (tissue transglutaminase Ab)

**N.B** NICE recommends that thyroid function tests are not necessary prior to making a positive diagnosis of IBS.

### **Management:**

The management of irritable bowel syndrome (IBS) is often difficult and varies considerably between patients. NICE issued guidelines in 2008

### **First-line pharmacological treatment - according to predominant symptom:**

- Pain: antispasmodic agents
- Constipation: laxatives but avoid lactulose
- Diarrhoea: loperamide is first-line

### **Second-line pharmacological treatment**

- Pinaverium (Dicetel® 50 mg Tab) is used to reduce the pain duration in IBS.
- Low-dose tricyclic antidepressants TCA e.g. Amitriptyline (Tryptizole ®) 5-10 mg are used in preference to SSRIs.

### **Other management options:**

- Psychological interventions - if symptoms do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile



(refractory IBS), consider referring for cognitive behavioural therapy, hypnotherapy or psychological therapy.

- Complementary and alternative medicines: 'do not encourage use of acupuncture or reflexology for the treatment of IBS'.

### **General dietary advice:**

- Have regular meals and take time to eat.
- Avoid missing meals or leaving long gaps between eating.
- Drink at least 8 cups of fluid per day, especially water or other non-caffeinated drinks such as herbal teas.
- Restrict tea and coffee to 3 cups per day.
- Reduce intake of alcohol and fizzy drinks.
- High soluble fibre diet.
- Consider limiting intake of high-fibre food (for example, wholemeal or high-fibre flour and breads, cereals high in bran, and whole grains such as brown rice).
- Reduce intake of 'resistant starch' often found in processed foods
- Limit fresh fruit to 3 portions per day
- For diarrhoea, avoid sorbitol
- Lactose-free diet.
- For wind and bloating consider increasing intake of oats (for example, oat-based breakfast cereal or porridge) and linseeds (up to one tablespoon per day).

### **Malabsorption**

Malabsorption is characterised by diarrhoea, steatorrhoea and weight loss. Causes may be broadly divided into intestinal (e.g. villous atrophy), pancreatic (deficiency of pancreatic enzyme production or secretion) and biliary (deficiency of bile-salts needed for emulsification of fats).

#### **Intestinal causes of malabsorption:**

- Coeliac disease
- Crohn's disease
- Tropical sprue
- Whipple's disease
- Giardiasis
- Brush border enzyme deficiencies (e.g. lactase insufficiency)

#### **Pancreatic causes of malabsorption:**

- chronic pancreatitis
- cystic fibrosis
- pancreatic cancer

### **Biliary causes of malabsorption:**

- biliary obstruction
- primary biliary cirrhosis

### **Other causes:**

- bacterial overgrowth (e.g. systemic sclerosis, diverticulae, blind loop)
- short bowel syndrome
- lymphoma

### **Whipple's disease**

Whipple's disease is **rare, multi-system** but potentially **fatal** condition and affects most commonly **middle-aged males 40-60 years**.

It can affect **any organ**, but dominated by involvement of **small bowel**, causing **malabsorption >> chronic diarrhoea**.

The causative organism is (**Tropheryma whippelii**), a Gm positive bacterium.

It is due to abnormal host immune response to the intracellular organism **Tropheryma whippelii**.

The main triad symptoms include: **weight loss (> 90%)**, **diarrhoea (> 70%)**, & **seronegative arthropathy (> 70%)**.

**Non-neurological manifestations** of Whipple's disease are more common and include **chronic diarrhoea**, malabsorption with steatorrhoea and associated abdominal distension and tenderness.

**Neurological manifestations** involve a chronic progressive impairment of higher **mental** function in association with **seizures**, myoclonus **ataxia** and **oculomasticatory myorhythmia** found uniquely in Whipple's.

**Cardiac** complications (in 30%) including: **pericarditis**, **Endocarditis valvular heart disease** and **conduction defects**.

**Pulmonary** involvements: pleurisy and lung infiltrates.

**Biochemical** abnormalities: **systemic inflammatory response** (high ESR & CRP) and **anaemia** and **Hypoalbuminaemia** due to malabsorption.

The diagnosis is made by **duodenal or jejunal biopsy** and demonstrating the **Tropheryma whippelii bacilli** within the mucosa on **PAS** staining.

Characteristically, there is accumulation of glycoprotein and fat filled periodic acid-Schiff (PAS +ve) **macrophage** within the **lamina propria** with **flattened mucosa** (**Macrophages with PAS stain +ve granules/sickle-like inclusion bodies**).

**Electron microscopy (E/M):** widened, flattened villi with small **Gram-positive bacilli** seen inside the macrophages.

**PCR DNA for Trophyrema Whipplei in the affected tissue:** it is **very diagnostic** and a best way to detect **remission** after prolonged therapy.

The disease is **fatal** if untreated, but there is usually a good response to antibiotic therapy (penicillin, tetracycline or sulphonamides)

**Treatment** is with **prolonged antibiotics**, for example, an initial **IV penicillin** and **streptomycin** for 2 weeks, followed by one year of **doxycycline**. Also co-trimoxazole can be used.

**Relapse** occurs in **30%** of patients and therefore **long-term follow-up** is essential.

EX: Middle-aged pt. attends clinic with his partner who tells you that he has **memory** problems + **chronic intermittent diarrhoea** over few months + limited vertical **eye** movements and exhibits rhythmic simultaneous eye and mouth movements + recurrent fever and arthralgia >> **Whipple's disease** due to intestinal infection with **Tropheryma whipplei**.

Creutzfeldt-Jakob disease (CJD) could also produce this picture, although myoclonus is usually more of a feature and cognitive impairment is more generalised and acute.

Whipple = **Chronic diarrhoea** (weight loss, steatorrhoea), **Neuro**, **Arthralgia**, **Pyrexia**, **Lymphadenopathy**.

### **Gastroenteritis**

- Gastroenteritis may either occur whilst at home or whilst travelling abroad (travellers' diarrhoea).
- Travellers' diarrhoea may be defined as at least 3 loose to watery stools in 24 hours with or without one of more of abdominal cramps, fever, nausea, vomiting or blood in the stool.
- The most common cause is *Escherichia coli*.
- Another pattern of illness is 'acute food poisoning'. This describes the sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin.

- Acute food poisoning is typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringens*.

Infection	Typical presentation
<b><i>Escherichia coli</i></b>	<u>Common</u> amongst <u>travellers</u> Watery stools Abdominal cramps and nausea
<b>Giardiasis</b>	<b>Prolonged</b> , non-bloody diarrhoea
<b>Cholera</b>	Profuse, watery diarrhoea Severe dehydration resulting in weight loss Not common amongst travellers
<b><i>Shigella</i></b>	<b>Bloody</b> diarrhoea Vomiting and abdominal pain
<b><i>Staphylococcus aureus</i></b>	Severe vomiting Short incubation period
<b><i>Campylobacter</i></b>	<p>A flu-like prodrome is usually followed by <b>crampy</b> abdominal pains frequently localising to the <b>right iliac fossa</b>, fever and <b>diarrhoea</b> which may be <b>bloody</b>.</p> <p>Usually arise from eating <b>undercooked frozen food</b> e.g. <b>barbeques</b>.</p> <p>Complications include <b>Guillain-Barre syndrome</b>, <b>Reactive arthritis</b> (Reiter's syndrome).</p> <p>The symptoms are usually self-limiting, lasting up to 5 days.</p> <p>TTT: <b>Supportive</b> as fluid replacement and anti-emetics, antibiotics is controversial: erythromycin.</p>
<b><i>Bacillus cereus</i></b>	<p>Two types of illness are seen</p> <ul style="list-style-type: none"> <li>• <b>Profuse vomiting</b> within <b>6 hours</b>, after eating <b>rice (Chinese restaurant)</b>.</li> <li>• Diarrhoeal illness occurring after 6 hours</li> </ul>

<b>Amoebiasis</b>	<b>Gradual</b> onset <b>bloody</b> diarrhoea, abdominal pain and tenderness which may last for several weeks
<b>Norovirus</b>	<u>Rapid</u> presentation within 12 hours, <u>severe unremitting vomiting</u> , diarrhoea, associated with a number of virtually <u>simultaneous cases</u> like in the same class, often during the <u>winter</u> months e.g. November. TTT: supportive (ORT).

**Incubation period:**

- 1-6 hrs: Staphylococcus aureus, Bacillus cereus\*
- 12-48 hrs: Salmonella, Escherichia coli
- 48-72 hrs: Shigella, Campylobacter
- > 7 days: Giardiasis, Amoebiasis

\*vomiting subtype, the diarrhoeal illness has an incubation period of 6-14 hours

**NB:** E. coli is the most common cause of travellers' diarrhoea and is usually a self-limiting condition, usually no treatment or investigation is required for this brief diarrhoeal illness.

**Cholera** and **giardiasis** are associated with **watery** diarrhoea.

**Giardia** is been reported as a cause of **chronic diarrhoea** with **weight loss**.

**Shigellosis** is a possible cause of **profuse bloody** diarrhoea.

Trophozoites and cysts are seen in acute amoebic dysentery, however cysts may also be excreted in asymptomatic carrier states.

**Bloody diarrhoea:** Campylobacter, then **Shigella** and **salmonella**.

**EX:** A group of workers presented to the ER with diarrhoea, flushing, sweating and a hot mouth. They fell ill **minutes** after eating lunch in the staff canteen. They had eaten **tuna fish**.

What is the likely cause of food poisoning?

**Scombroid poisoning** is associated with consumption of Scombridae, dark meat fish such as tuna, mackerel and marlin.

The most common cause of scombroid poisoning is due to ingestion of spoiled fish following inadequate refrigeration or prolonged time at room temperature. Cooking does not inactivate the toxin/histamines.

**Scombrototoxin food poisoning** is caused by the ingestion of foods that contain high levels of histamine and possibly other vasoactive amines and compounds. Histamine and other amines are formed by the growth of certain bacteria and the subsequent action of their decarboxylase enzymes on histidine and other amino acids in food, by spoilage of foods such as **fishery** products, particularly **tuna** or mahi mahi. Incubation period is **10-60 minutes**.

The definition of **chronic diarrhoea** is the abnormal passage of **3 or more** loose or liquid stools per day for **more than 4 weeks** and/or **a daily stool volume > 200 ml/day (weight > 200 g/day)**.

**Traveller diarrhoea:**

- It is usually caused by **enterotoxigenic E.coli** or **rota virus**.
- E.coli usually produce copious diarrhoea with minimal fever.
- It is not helpful to send stool culture.
- TTT:
  - Main ttt to **drink large amount of oral fluids**.
  - You should start **antibiotics** if the condition persist for > 3 days.
  - **Ciprofloxacin ± Loperamide**

**Haemolytic uraemic syndrome (HUS).**

The presence of **thrombocytopenia** and evidence of **haemolysis** in association with **bloody diarrhoea** should make you think of haemolytic uraemic syndrome (HUS).

HUS is the **triad** of:

- 1) Microangiopathic haemolytic anaemia (MAHA)
- 2) Thrombocytopenia, and
- 3) Acute kidney injury.

It is classically associated with **Escherichia coli O157:H7**, which produces a Shiga verotoxin.

Approximately **15%** of cases with *Escherichia coli* O157 will develop HUS. It can occur up to 2 weeks following the initial onset of symptoms and can present after recovery from the acute illness.

The incubation period of *Escherichia coli* O157 is 1 to 6 days.

HIV, *Streptococcus pneumoniae*, *Shigella dysenteriae* and Coxsackie virus can also result in HUS, but much less commonly.

The verotoxin circulates and binds to endothelial receptors, particularly in the kidney, GIT and CNS, resulting in the deposition of thrombin and fibrin in the microvasculature.

Haemolysis subsequently occurs as erythrocytes travel through the affected vessels. Platelets are sequestered resulting in lower circulating numbers.

Treatment for HUS is primarily **supportive** with fluid and electrolyte management, **antihypertensive** therapy and **dialysis** where required.

**Plasma exchange** can also be used to try to remove circulating toxin.

### **Clostridium difficile**

*Clostridium difficile* is a **Gram positive anaerobic rod** often encountered in hospital practice.

It produces an **exotoxin** (toxin A and toxin B) which causes intestinal damage leading to a syndrome called **pseudomembranous colitis**.

*Clostridium difficile* develops when the normal gut flora are suppressed by **broad-spectrum antibiotics**.

Symptoms are typically said to occur **5-10 days after** commencing antibiotic.

**Clindamycin** is historically associated with causing *Clostridium difficile* but the aetiology has evolved significantly over the past 10 years.

**Second** and **third** generation **cephalosporins** are **now** the leading cause of *Clostridium difficile*. Also **penicillins** and **quinolones**.

Less commonly: macrolides, trimethoprim and sulphonamides have been reported to cause the disorder.

Aminoglycosides, tetracyclines and chloramphenicol are rarely associated with pseudomembranous colitis.

Sigmoidoscopy is not used routinely, but can reveal distal ulceration and possible yellow slough or pseudo membrane in around half of patients.

Mortality is high in elderly patients it may be as high as 10%.

#### Features:

- Diarrhoea
- Abdominal pain
- A raised white blood cell count is characteristic
- If severe toxic megacolon may develop

Features suggestive of **severe** *C. diff* infection include

- 1) **Temperature** greater than 38.5°C
- 2) **WCC** >15
- 3) Severe abdominal pain
- 4) **Hypovolaemia (low BP)**
- 5) Lactic acidosis.

Diagnosis: detecting **Clostridium difficile toxin (CDT)** in the **stool**.

Management:

- First-line therapy is **oral metronidazole** for **10-14 days**.
- If severe or not responding to metronidazole then **oral vancomycin** may be used, and it has no systemic absorption.
- For life-threatening infections a **combination** of oral vancomycin and IV metronidazole should be used.
- Teicoplanin and Rifampicin have both been used in patients who fail to respond to first line therapy.
- Cholestyramine may be useful in reducing severe diarrhoea.

**NB**: **Plain AXR** is useful for **diagnosing toxic dilatation** and would be the investigation of choice in patient with abdominal distension. Toxic dilatation should be excluded **prior** to sigmoidoscopy. However it does not establish the diagnosis.

**NB**: If **sigmoidoscopy** done>>>> will shows multiple white plaques adhered to the gastrointestinal mucosa.

The major pharmacologic advantage of oral vancomycin over metronidazole is that **oral vancomycin is not absorbed**, so **maximal concentrations** of the drug can act intracolonicallly at the site of infection.

IV Metronidazole can be used where oral administration is impossible.

IV Vancomycin is not effective.

The instillation of **intracolonic vancomycin (as a retention enema)** is sometimes used as an adjunct to the treatment of severe disease.



### Carcinoid syndrome

#### Carcinoid tumours:

- It is a neuroendocrine tumours, which originate from **enterochromaffin** cells of the **intestine**.
- Usually occurs when metastases are present in the liver and release serotonin (5-HT) into the systemic circulation which will cause **flushing**, **diarrhoea** and **bronchospasm**.
- They are indolent tumours secreting more than 20 different hormones, likely 5-HT, kinins, prostaglandins and other vasoactive substances are secreted.
- Most of cases with more than **95%** of patients with carcinoid tumour have **liver metastasis** at the time of diagnosis.
- The carcinoid syndrome **only** arises **when liver metastases are present** and the tumour products being metabolised by the liver by draining directly into the hepatic veins.
- May also occur with lung carcinoid as mediators are not 'cleared' by the liver.
- The most common sites for the primary tumour are the **appendix (40%)**, **terminal ileum (30%)**, **rectum (20%)**, and less commonly in the bronchus, ovary and testis.
- 80% of tumours greater than 2 cm in diameter will metastasize.
- **Very bad prognosis: average survival is 5-10 years from diagnosis**

#### Features:

- **Flushing** (often **earliest** symptom) in **75-90%** of cases, it is caused due to release of vasoactive compounds such as 5-HT and bradykinin, it is often provoked by alcohol.
- **Hypotension**
- Chronic diarrhoea (in > **70%**).
- Bronchospasm (in **25%**).
- Right heart valvular stenosis e.g. tricuspid regurgitation / pulmonary stenosis is found in **50%** of cases and can lead to right-sided CHF like LL oedema (left heart can be affected in bronchial carcinoid).
- Pellagra can rarely develop as dietary tryptophan is diverted to serotonin by the tumour.

- Other molecules such as ACTH and GHRH may also be secreted resulting in, for example, Cushing's syndrome.

The **triad** of **facial flushing**, **chronic diarrhoea** and **cardiac** involvement represents more than **85%** of symptoms of carcinoid syndrome.

#### Investigations:

- **High 24-hour urinary 5-HIAA excretion:** (5-hydroxyindoleacetic acid) - is greater than 0.3 mmol.
- **Abdominal US:** to visualise the liver metastasis.
- **Chest and abdomen CT**
- Plasma chromogranin A y

#### Management: (mainly palliative):

- Somatostatin analogues e.g. Octreotide
- Symptomatic control, as diarrhoea: cyproheptadine may help
- Surgery to debulk the tumour
- Trans-arterial embolisation and radioisotope therapy.

**EX:** A 65-year-old man known to have a carcinoid tumour of the appendix is found to have hepatic metastases. If the patient develops carcinoid syndrome, what is the first symptom most likely to occur? >>> **Flushing.**

**NB:** The worst prognostic feature in carcinoid syndrome is **valvular** heart disease. Cardiac lesions are not reversible with treatment, deteriorate with time and frequently require replacement. Most patients die of progressive right heart failure within one year after onset of symptoms.

#### **Colorectal cancer (CRC): genetics**

It is currently thought there are three types of colon cancer:

- 1) **Sporadic** (**95%**)
- 2) Hereditary non-polyposis colorectal carcinoma (**HNPCC**, 5%)
- 3) Familial adenomatous polyposis (**FAP**, <1%)

Studies have shown that **sporadic colon** cancer may be due to a series of genetic mutations. For example, more than 50% of colon cancers show allelic loss of the APC gene. It is believed a further series of gene abnormalities e.g. activation of the

K-ras oncogene, deletion of p53 and DCC tumour suppressor genes lead to invasive carcinoma.

**HNPCC**, an autosomal dominant condition characterized by early onset CRC with strong positive family history, is the most common form of inherited colon cancer. Around 90% of patients develop cancers, often of the proximal colon, which are usually poorly differentiated and highly aggressive. Individuals at risk should be offered colonoscopy screen at 2 years interval from the age of 20 years. Currently 7 mutations have been identified, which affect genes involved in DNA mismatch repair leading to microsatellite instability. The most common genes involved are:

- **MSH2** (60% of cases)
- **MLH1** (30%)

The **Amsterdam criteria** for **HNPCC** are sometimes used to aid diagnosis:

- 1) At least **3 family members** with colon cancer, **one** of them is **first** degree relative.
- 2) The CRC affecting at least **two generations**.
- 3) At least one case diagnosed **before the age of 50 years**.

**FAP** is a rare autosomal dominant condition which leads to the formation of hundreds of polyps by the age of 30-40 years. Patients inevitably develop carcinoma. It is due to a **mutation** in a **tumour suppressor gene** called adenomatous polyposis coli gene (APC), located on chromosome 5. Genetic testing can be done by analysing DNA from a patient's white blood cell. Patients generally have a total colectomy with ileo-anal pouch formation in their twenties.

Physical features associated with this condition includes congenital hypertrophy of the retinal pigment epithelium, dental abnormalities including supernumerary teeth and dentigerous cyst, Osteomas of the skull and mandible, fibromas and epidermoid cysts in prepubescent patients.

Patients with FAP are also at risk from duodenal tumours. A variant of FAP called Gardner's syndrome can also feature Osteomas of the skull and mandible, retinal pigmentation, thyroid carcinoma and epidermoid cysts on the skin.

<b>FAP</b> is caused by <b>loss</b> of the <b>APC gene</b> on the <b>long arm</b> of chromosome <b>5</b> .
--

In cancer colon >> the <b>rectum</b> and <b>sigmoid</b> colon are the commonest sites, not the ascending colon.
---

### Hamartomatous polyposis syndrome

**Multiple hamartomatous polyps** in GIT by endoscopy suggest the presence of one of the **hamartomatous polyposis syndrome**:

- 1) Familial juvenile polyposis.
- 2) Cowden's syndrome: (see below)
- 3) Peutz-Jeghers syndrome
- 4) Neurofibromatosis type I
- 5) MEN syndrome type II b

These syndromes are distinct from **the more common adenomatous syndromes** like

- 1) HNPCC (Hereditary non-polyposis colon cancer) and
- 2) FAP (Familial adenomatous polyposis).

### Cowden's syndrome:

- **Multiple hamartomatous polyps in GIT**
- With characteristic **mucocutaneous lesions** such as oral mucosal papillomas, palmoplantar keratosis, trichilemmomas (benign tumour of hair follicles).
- It is important to **diagnose early** because of the high risk of **malignancy**, particularly of breast and thyroid.
- **Thyroid dysfunction** is common even in the absence of cancer.

### Gardener's syndrome:

It is a **rare** familial **autosomal dominant** condition characterized by **multiple small and large** intestinal **polyposis** tumours + **Osteomas** + **soft tissue tumours** (multiple lipomas, fibromas, and epidermoid cysts).

It carries an increased risk of **papillary carcinoma of the thyroid**.

**Colonic carcinoma** develops in 7% of individuals by age 21 years, 50% by age 39 years and 90% by age 45 years.

**Colectomy** is recommended once polyps appear.

### Colorectal cancer: referral guidelines

NICE recommend the following patients are referred urgently (i.e. within 2 weeks) to colorectal services for investigation:

- Patients > 40 years old, reporting rectal bleeding with a change of bowel habit towards looser stools and/or increased stool frequency persisting for 6 weeks or more.

Patients > 60 years old, with rectal bleeding persisting for 6 weeks or more without a change in bowel habit and without anal symptoms.

- Patients > 60 years old, with a change in bowel habit to looser stools and/or more frequent stools persisting for 6 weeks or more without rectal bleeding.
- Any patient presenting with a right lower abdominal mass consistent with involvement of the large bowel.
- Any patient with a palpable rectal mass.
- **Unexplained iron deficiency anaemia in men or non-menstruating women** (Hb < 11 g/dl in men, < 10 g/dl in women).

#### National Health Service guidelines on screening for bowel cancer:

- The national bowel cancer screening programme is **open to men and women between the ages of 60 and 74**.
- Individuals are invited to complete a faecal occult blood (**FOB**) test every **2 years**.
- A **single** positive result will trigger an invitation to attend a consultation to consider colonoscopy.
- An uncertain or unclear FOB result will result in a request to **repeat** up to a maximum of 2 further tests.
- If persistent unclear results require further investigation with consideration of colonoscopy.
- A **negative** faecal occult blood does **not** exclude an underlying diagnosis of colorectal cancer.
- Any patient with symptoms, irrespective of a negative faecal occult blood test, should be investigated for the possibility of underlying bowel cancer as appropriate.

#### The relationship between type 2 diabetes and colonic cancer:

**Type 2 DM** is associated with a **40-60% increase** in the risk of cancer of the **large** bowel. This increase is **linked to changes in HbA1c**.

Type 2 DM is associated with significantly higher rates of overall mortality and reduced disease free and recurrence free survivals after chemotherapy/radiotherapy and **insulin has not been shown to have any effects on mortality**.

**No association has been found between colonic malignancy and type 1 DM, nor gestational diabetes (GDM).**

**Increased concentrations of C peptide** are a **marker of increased colorectal cancer risk**.

A number of studies have independently linked **high** circulating concentrations of **C peptide**, as a marker of insulin production, with increased colorectal cancer risk. The molecular basis has not been proven but it may be reasonable to extrapolate it is linked to the growth stimulation effects of insulin.

**Colorectal carcinoma** is the **third** most common cancer in the UK, after breast and lung, 75% of cases occur in people aged over 65 years.

Around 50% survive for over 5 years following diagnosis, but it remains the **second most common cause of cancer death in the UK**.

The UK now has a national screening programme for those **over 60 years**, which uses **faecal occult blood (FOB)** testing.

With regard to the investigation of colorectal carcinoma, **colonoscopy** should be offered to patients without major co-morbidity.

If a lesion suspicious of cancer is detected, a **biopsy** should be performed to obtain a histological diagnosis.

If the colonoscopy is incomplete, it should be repeated or CT colonography or barium enema should be performed.

**Flexible sigmoidoscopy** then **barium enema** should be offered for patients with **major co-morbidity** e.g. like IHD with CHF.

**CT colonography** is an alternative if the local radiology service is competent in this technique. A small dose of oral contrast is administered 24 hours prior to the procedure and then the colon is imaged using helical CT scanning. Most CT colonography protocols require the use of bowel cleansing agents. The advantages over colonoscopy include no requirement for sedation, smaller risk of perforation, and extra-colonic pathology can also be demonstrated.

If a lesion suspicious of cancer is detected on CT colonography, a colonoscopy and biopsy should be offered (unless there are absolute contraindications).

**CT chest, abdomen, pelvis** should be offered after the diagnosis is made to estimate the stage of the disease.

Patients with a **rectal** tumour should also undergo **MRI** to assess local disease. **Endorectal ultrasound** can then be offered if MRI shows disease amenable to local excision (or if MRI is contraindicated). Digital rectal examination is not part of the staging investigations.

### Peutz-Jeghers syndrome (PJS)

Peutz-Jeghers syndrome is an **autosomal dominant** condition caused by a germline **mutation** of the **STK11** (serine threonine kinase 11) gene, usually located on the long arm of chromosome **19**.

PJS is characterised by **numerous hamartomatous polyps** in the gastrointestinal tract (stomach and large intestine).

The polyps only rarely undergo malignant change.

It is also associated with **pigmented freckles** on the lips, face, palms, soles and perianal skin. It is usually (90%) associated with **peri-oral pigmentation**.

Around **50%** of patients will have **died** from a **GIT cancer** by the age of **60** years.

Colon cancer is the most common type of gastrointestinal cancer that patients with Peutz-Jeghers syndrome develop.

There is an association with non-GIT malignancies like endometrial, ovarian & lung.

#### Genetics:

- Autosomal dominant (AD)
- Responsible gene encodes serine threonine kinase **LKB1** or **STK11**

#### Features:

- 1) **Hamartomatous polyps in GI tract** (mainly small bowel)
- 2) **Mucocutaneous melanocytic macules**: Pigmented lesions on lips, oral mucosa, face, palms and soles
- 3) Intestinal obstruction e.g. intussusception
- 4) Gastrointestinal bleeding >>> **Fe Def. Anemia**.

#### Management:

- Conservative unless complications develop

Pts with Peutz-Jeghers syndrome require **colonoscopy every 2 years** after the age of 25 years for evaluation of the presence of polyps and polypectomy.

**NB:** Osteomas are a feature of Gardner's syndrome, a variant of familial adenomatous polyposis (FAP), not present in Peutz-Jeghers syndrome.

Defective mismatch repair genes **hMSH2** and **hMLH1** leads to hereditary non-polyposis colorectal cancer (**HNPCC**).

Mutation of **APC** gene leads to familial adenomatous polyposis (**FAP**).

Mutation of **STK11/LKB1** gene is with Peutz-Jeghers syndrome (**PJS**)

### Angiodysplasia

Angiodysplasia is a **vascular** deformity of the gastrointestinal tract which predisposes to bleeding and iron deficiency anaemia.

Angiodysplasia is generally seen in **elderly** patients.

There is thought to be **an association with aortic stenosis**, although this is debated.

It may be found **throughout** the GIT, although it most commonly occurs in the **caecum** and **ascending colon**.

It is a significant cause of **chronic** anaemia and can also cause **acute** haemorrhage.

Diagnosis:

- 1) **Colonoscopy.**
- 2) **Capsule endoscopy**
- 3) Mesenteric angiography if acutely bleeding.

Management:

- Endoscopic **cautery** or **argon plasma photo coagulation (APPC)**.
- **Embolisation** of the bleeding vessel during **angiography**.
- **Surgical resection.**
- Antifibrinolytics e.g. Tranexamic acid.
- Oestrogens may also be used.

**EX:** A 67-year-old man presents with shortness-of-breath. He has a past history of **aortic stenosis** but is otherwise well. On examination he has a systolic murmur and a clear chest. Routine bloods shows: **Hb 8.7 gm%, low MCV** >>> this patient most likely has **angiodysplasia** which has a known association with aortic stenosis >>for **colonoscopy**.



**EX:** Old male 66 years old with bleeding per rectum and Hb is 8 gm%, gastroscopy and Ba enema are normal >>>?? **Angiodysplasia >>> Capsule enteroscopy or Mesenteric angiography: abnormal vascular blush in the ascending colon.**

After **diverticulosis**, **angiodysplasia** is the second leading cause of **lower GI** bleeding in patients **older than 60 years**.

### Anal fissure

Anal fissures are longitudinal or elliptical tears of the squamous lining of the distal anal canal.

If present for less than 6 weeks they are defined as acute, and chronic if present for more than 6 weeks.

Around 90% of anal fissures occur on the **posterior midline**.

#### Management of an acute anal fissure (< 6 weeks):

- Dietary advice: high-fibre diet with high fluid intake.
- Bulk-forming laxatives are first line - if not tolerated then lactulose should be tried.
- Lubricants such as petroleum jelly may be tried before defecation
- Topical anaesthetics-analgesia

**NB:** topical steroids do not provide significant relief

#### Management of a chronic anal fissure (> 6 weeks):

- The above techniques should be continued
- Topical glyceryl trinitrate (GTN) is first line treatment for a chronic anal fissure.
- If topical GTN is not effective after 8 weeks then secondary referral should be considered for surgery or botulinum toxin.

Chronic Anal fissure (> 6 wks.) >>> topical glyceryl trinitrate (GTN)

### Small bowel bacterial overgrowth syndrome (SBBOS)

SBBOS is a disorder characterised by excessive amounts of bacteria in the small bowel resulting in gastrointestinal symptoms.

**B<sub>12</sub> deficiency (macrocytic anaemia)** is caused by bacterial overgrowth.

It is very unusual in patients without risk factors for the condition.

**Steatorrhoea** and **flatulence** are classic presenting features of SBBOS.

**Risk factors for SBBOS:**

- **Neonates** with congenital gastrointestinal abnormalities
- **DM**
- **Inflammatory bowel disease (IBD: CD/UC)**
- **Diverticulosis**
- **Scleroderma**

It should be noted that many of the **features** **overlap** with **IBS**:

- Abdominal pain
- Bloating, flatulence
- **Chronic diarrhoea**

**Diagnosis:** Hydrogen breath test after giving lactose or glucose.

**Management:**

- 1) Correction of underlying disorder.
- 2) Antibiotic therapy:
  - a. **Rifaximin**, a non-absorbable form of Rifampicin, is now the treatment of **choice** due to relatively low resistance.
  - b. Co-amoxiclav or metronidazole or tetracyclines is also effective in the majority of patients.
- 3) If this fails, jejunal aspiration is recommended to identify the organism.

**N.B** Tetracyclines are no longer commonly used due to widespread bacterial resistance.

**EX:** Male pt. 70 years old with **left iliac fossa tenderness**, **fever**, **intermittent diarrhoea**, **High TLC**, **Urine:** red cells +, white cells + (due to periureteric inflammation) >>> **Diverticulitis** >>> **CT** to assess severity, degree of local infiltration, possible perforation or abscess formation. Medical ttt by **IV antibiotics** and surgical opinion is crucial.

### Gastrointestinal physiology: enzymes

**Amylase** is present in saliva and pancreatic secretions. It breaks starch down into sugar.

The following brush border enzymes are involved in the breakdown of carbohydrates:

- **Maltase**: cleaves disaccharide maltose to glucose + glucose
- **Sucrase**: cleaves sucrose to glucose and fructose
- **Lactase**: cleaves disaccharide lactose to glucose + galactose

Brush border enzymes:

- **Maltase**: glucose + glucose
- **Sucrase**: glucose + fructose
- **Lactase**: glucose + galactose

### Lactose intolerance

Lactase acts on lactose to generate glucose and galactose.

Lactose intolerance is least common in white northern Europeans and is more common in **Asian**, and **East Asian** races.

Lactose intolerance may be diagnosed with a **DNA assay of the lactase gene** along with a **hydrogen breath test**.

Any **GI infection** (e.g. **Rotavirus** infection) may reveal lactose intolerance as gut flora may be altered by large bowel bacterial or viral load, as well as the treatment of infection.

A change from an Eastern to a Western high lactose diet may also reveal lactose intolerance.

Many patients labelled as having IBS may suffer from undiagnosed lactose intolerance and many medications use lactose as a binding and stabilising agent.

Treatment of lactose intolerance is with **careful replacement of lactase**.

### Mesenteric ischaemia

Mesenteric ischaemia is primarily caused by arterial embolism resulting in **infarction of the colon**.

It is more likely to occur in areas such as the splenic flexure that are located at the borders of the territory supplied by the superior and inferior mesenteric arteries.

Predisposing factors:

- increasing age
- atrial fibrillation
- other causes of emboli: endocarditis
- cardiovascular disease risk factors: smoking, hypertension, diabetes

Features:

- abdominal pain
- rectal bleeding
- diarrhoea
- fever
- bloods typically show an elevated WBC associated with acidosis

Management:

- supportive care
- laparotomy and bowel resection

### Melanosis coli (Surreptitious laxative abuse)

Melanosis coli is a disorder of pigmentation of the bowel wall, dark pigmentation of the colon by colonoscopy.

Histology demonstrates pigment-laden macrophages.

It is associated with laxative abuse, especially anthraquinone compounds such as **senna**.

It is typically over-represented in **young, female** patients and usually closely linked to **eating disorders** (Bulimia and Anorexia) or **psychiatric illness**.

Patients may well present to medical services and be referred on to secondary care with symptoms relating to overuse of laxative agents. They may well also **deny** abusing any medications on initial questioning.

Diarrhoea - biopsy shows pigment laden macrophages = laxative abuse

**Chronic small bowel ischaemia (Intestinal angina) (ischaemic colitis):**

It is an uncommon condition that usually occurs in **elderly** smokers with evidence of **vascular** disease elsewhere (CAD, TIA or PVD)

It is rarely seen in patients below the age of 60.

C/O: **post-prandial colicky abdominal pain** within 30-60 minutes, **bloody diarrhoea, rectal bleeding** (altered blood mixed with stool) and **weight loss** (due to combination of fear of eating due to pain and malabsorption)

**Pain** that is **disproportionately severe** compared to the abdominal findings is characteristic.

Diagnosis is difficult and usually made by **CT with mesenteric angiography**.

**Ba enema** or **CT with double contrast: Thumb printing** being indicative of **mucosal oedema**.

If undiagnosed, it may progress to **acute intestinal ischaemia** which has a **high mortality** of approximately **80%**.

**Vascular reconstruction** is sometimes possible.

**Microscopic colitis**

It is defined by the triad of

- 1) **Watery diarrhoea**
- 2) **Normal colonoscopy**
- 3) Increased **cellular** inflammation at **lamina propria**

It is a **histological diagnosis** with **macroscopically normal colon mucosa**.

It is an uncommon disease with an incidence of 5/100,000 per year and frequents **older** patients (mean age **55-65**) and **women**.

There is a **link** with **NSAIDs, H2 blocker** and **PPI**.

TTT:

- **Stopping** the offending medications.
- Corticosteroids, azathioprine, cholestyramine and now bismuth have been used as a ttt with some effects in patients who did not respond adequately to cessation of the causative agent.

**Amoebic liver abscess:**

C/O: Fever, RUQ abdominal pain with tenderness hepatomegaly and weight loss in **endemic tropical** countries. It can be **indistinguishable** from pyogenic abscess.

It can often present **without bowel changes** in up to **50%** of cases.

**Serum anti Entamoeba histolytica antibody** can be found in over **95%** of cases, but this could be **past** or **present** infection.

**Stool antigen detection** may be helpful and facilitates early diagnosis before an antibody response occurs (< 7 days) and differentiates pathogenic from non-pathogenic Entamoeba infection.

TTT:

- **Metronidazole** for **10 days** is the drug of choice rather than albendazole.
- For **large** abscess **aspiration** is the intervention of choice, combined with antibiotic therapy.

**Hydatid liver disease**

It is uncommon in Europe and USA but common in **Middle East** and **South America** and in **sheep-rearing** areas such as **Australia, China, Japan and Russia**.

Hydatid cyst is often **asymptomatic**, but can present with hepatomegaly, obstructive jaundice, fever and cholangitis.

Abdomen US and CT: Liver is the most common site.

**Serology is neither sensitive nor specific.**

TTT: **High dose oral Albendazole** 10 mg/kg for 1-3 months followed by **percutaneous aspiration** of the cysts and **sterilisation** with alcohol or hypertonic saline.

**D.D. Causes of Chronic diarrhoea:**

- 1) **Coeliac** disease.
- 2) **IBD** (CD & UC).
- 3) **Whipple** disease.
- 4) **Tropical sprue**
- 5) **Chronic pancreatitis**.
- 6) **VIPoma**.
- 7) **Carcinoid** tumour.

- 8) **Bacterial overgrowth** syndrome.
- 9) **Microscopic colitis**
- 10) **Thyroid** disorder.
- 11) **HIV**.
- 12) **CMV**-associated colitis.
- 13) **Drugs**: broad spectrum antibiotics, Diuretics, Digoxin, some cholesterol lowering agents, Depakin, Thyroxine, Levodopa, Antacids, PPI (lansoprazole), Theophylline, Colchicine, NSAIDS and oral hypoglycaemic drugs.

### Constipation

Patients referred to hospital with constipation tend to be those with more **severe impairment of quality of life** and who have **failed trials** of dietary high fibers supplementation or laxatives.

Up to **50%** of **women** who present with constipation are victims of **sexual or physical abuse**, therefore it is important to take a good **social** history.

**Abdominal radiography** is important to exclude a dilated colon caused by megacolon or Hirschsprung's disease.

**Whole gut radio-opaque transit study** is the most appropriate next management step, it measures **generalized intestinal motor function**, and it is non-invasive and easy to interpret.

Colonoscopy or barium enema is helpful only in excluding primary colonic cause of constipation and is **not** always necessary in the **young**.

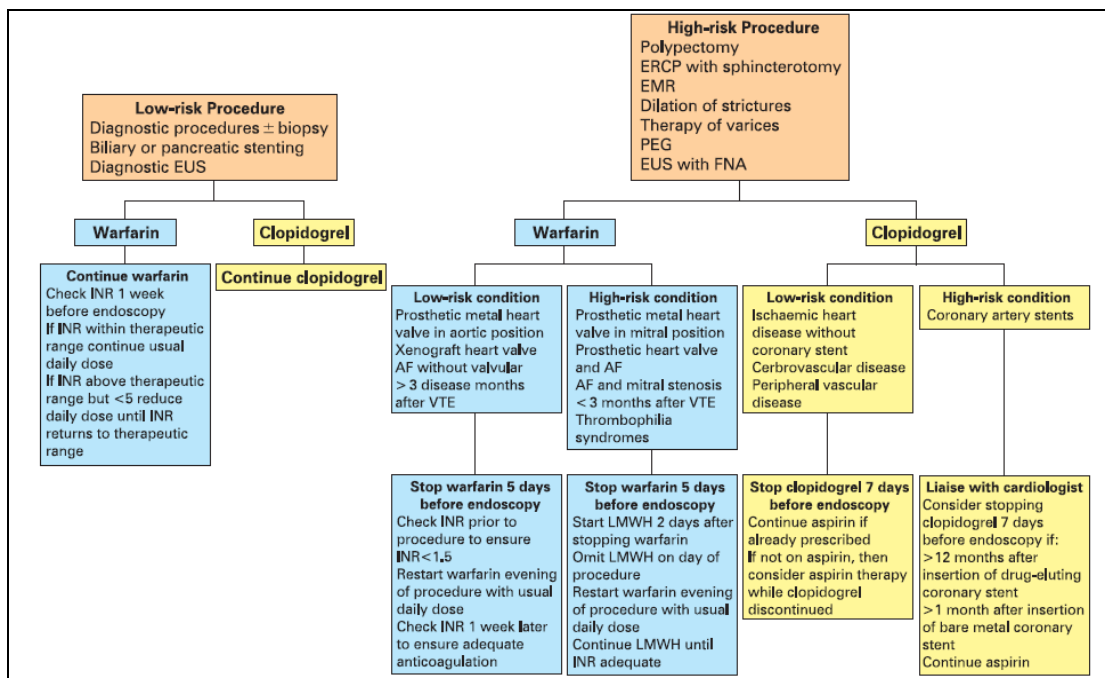
**Drugs** that induce constipation: Iron, CCBs, opiates, antidepressants and antipsychotics.

TTT:

- **“Combination compounds”** include bulking agents, stimulant laxatives, faecal softeners and osmotic laxatives.
- If the above fails, **“biofeedback”** has been shown to be useful in certain groups of patients.

**Guidelines for the management of anticoagulant and antiplatelet therapy in patients undergoing endoscopic procedures.**

- ERCP with sphincterotomy is an endoscopic procedure with a high risk of haemorrhage.
- Clopidogrel is associated with a much higher risk of bleeding than aspirin.
- Ischaemic heart disease without endovascular stents is considered a low risk condition for the temporary discontinuation of clopidogrel.
- Aspirin and clopidogrel are both irreversible inhibitors of platelet function and when they are to be discontinued must be stopped at least 7 days prior to procedure to significantly reduce the risk of associated bleeding.
- Aspirin is not associated with the same degree of bleeding as clopidogrel and may be continued in those already taking it even prior to endoscopic intervention with a high risk of bleeding.
- In those not already prescribed aspirin it should be considered as a bridging agent if clopidogrel must be discontinued.
- Patients with coronary stents in place are at high risk of thrombosis if clopidogrel is discontinued. Their management should be in conjunction with a cardiologist.
- The risk of thrombosis and thus stopping clopidogrel is reduced if more than 12 months have elapsed since insertion of a DES or more than one month after insertion of a BMS.



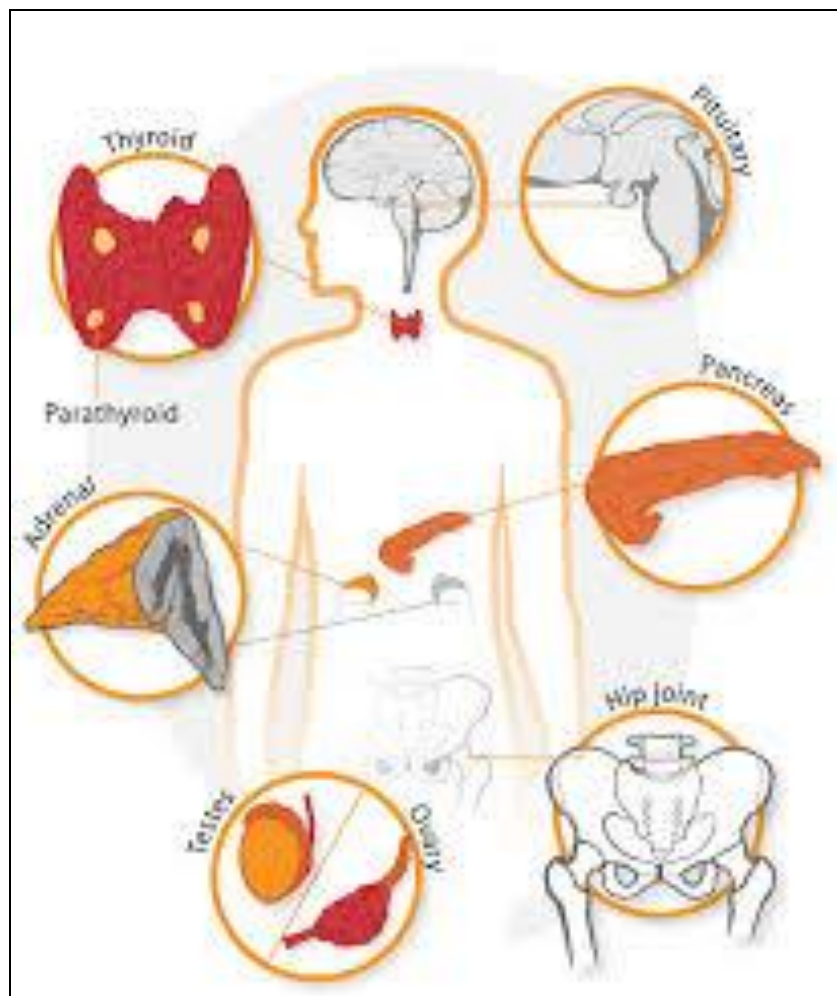


### Miscellaneous

For assessment of nutritional status >>> **Mid-arm muscle circumference** and **skin-fold thickness**.

**Radiation enteritis**: radiation injury to the rectum and sigmoid colon is commonly seen following ttt of cancers of the cervix, uterus, prostate and bladder. It often occurs 9 to 14 months following radiation exposure and results in chronically ischaemic intestinal segment that may lead to stricture.

# Endocrinology



**Diabetes: pathophysiology****Type 1 DM:**

- Autoimmune disease.
- Type 1 DM is a primarily **T cell mediated disorder**. Whilst autoantibodies to beta cell antigens are measurable in patients with the disease, they are not thought to play direct role in its pathogenesis.
- Antibodies against beta cells of pancreas.
- Various antibodies such as islet-associated antigen (IAA) antibody and glutamic acid decarboxylase (GAD) antibody are detected in patients who later go on to develop T 1 DM - their prognostic significance is not yet clear.
- Anti-IA2 and anti-GAD Abs are measured to support the diagnosis.
- **Only 10%** of patients have a positive family history.
- Identical twins show a genetic concordance of 40%.
- HLA DR4 > HLA DR3.
- It is inherited in a polygenic fashion.
- Enteroviruses may play a role in both protection from and susceptibility to T1DM.
- The presence of **GAD** autoantibodies would signify an autoimmune aetiology and their presence signifies a 10 fold increased risk of developing IDDM, **being found in 70-90% of type1 diabetics**. This would be a case of latent autoimmune diabetes in adults (**LADA**) and constitutes approximately 10% of patients incorrectly labelled as T2DM.
- The most closely associated with the imminent development of DM T1 is **loss of first phase insulin response** which is an indicator of significant impending beta cell destruction.

**Type 2 DM:**

- It is thought to be caused by a relative deficiency of insulin and the phenomenon of insulin resistance.
- A reduction in beta cell mass due to **amyloid** deposition may partly account for this.
- The presence of **amyloid polypeptide** on pancreatic histology is highly suggestive of type 2 DM.
- Age, obesity and ethnicity are important aetiological factors.
- There is almost 100% concordance in identical twins and **no HLA associations**.

### Diabetes mellitus: diagnosis

The following is based on the (WHO) 2006 guidelines:

#### To diagnose Diabetes mellitus:

##### If the patient is symptomatic plus:

- **Fasting** glucose  $\geq 7.0$  mmol/l. (= 125 mg/dl)
- **Random** glucose  $\geq 11.1$  mmol/l (= 200 mg/dl) or
- 2 hrs after 75g oral glucose tolerance test OGTT:  $\geq 11.1$  mmol/l (= 200 mg/dl)

If the patient is asymptomatic the above criteria apply but must be demonstrated on TWO confirmatory samples on separate occasions.

Diagnosis of DM: symptoms + fasting  $\geq 7.0$ , random  $\geq 11.1$  - if asymptomatic need two readings.

The diagnosis of diabetes requires (WHO guidelines):

- **Fasting** plasma glucose  $\geq 7.0$  mmol/l ( $\geq 125$  mg/dl).
- **Random** plasma glucose  $\geq 11.1$  mmol/l ( $\geq 200$  mg/dl)
- **75 g OGTT two hour** plasma glucose  $\geq 11.1$  mmol/l ( $\geq 200$  mg/dl).

The American Diabetes Association (ADA) has recently added another criterion:

- **HbA1c  $>6.5\%$  or 48 mmol/mol.**

In 2011 WHO released supplementary guidance on the use of HbA1c on the diagnosis of diabetes:

- A HbA1c of greater than or equal to 6.5% (48 mmol/mol) is the cut-off point for a diagnosis of diabetes mellitus.
- A HbA1c value of less than 6.5% does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes).
- In patients without symptoms, the test must be repeated to confirm the diagnosis.
- It should be remembered that misleading HbA1c results can be caused by increased RBCs turnover (as in anaemia, haemoglobinopathies and pregnancy).

### Impaired Glucose Regulation (IGR)

Impaired glucose regulation (IGR) may also be referred to as non-diabetic hyperglycaemia (NDH) or **prediabetes**.

It describes blood glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus.

Diabetes UK estimate that around 1 in 7 adults in the UK have IGR.

Many individuals with IGR will progress on to developing T2DM and they are therefore at greater risk of microvascular and macrovascular complications.

There are two main types of IGR:

- 1) Impaired fasting glucose (IFG) - due to hepatic insulin resistance.
- 2) Impaired glucose tolerance (**IGT**) - due to muscle insulin resistance.

Patients with **IGT** are more likely to develop T2DM and cardiovascular disease than patients with IFG.

The absolute **risk of progression from IGT to type 2 DM** is **33 % over 6 years** follow up. This increased to 65% if individuals had both IGT and IFG.

**Triglycerides** is the **strongest independent** predictor of **cardiovascular death** in a patient with **impaired glucose tolerance IGT**, ahead of other more established risk factors such as smoking, body weight or blood pressure.

Definitions:

- **Impaired fasting glucose (IFG):** A fasting glucose from 6.1 to 7.0 mmol/l. (= from 110 to 125 mg/dl).
- **Impaired glucose tolerance (IGT):** A fasting plasma glucose < 7.0 mmol/l and OGTT 2-hour value from **7.8** mmol/l to 11.1 mmol/l (= from 140 to 200 mg/dl).
- The role of HbA1c in diagnosing IGR and diabetes is currently under review.
- People with IFG should then be offered an oral glucose tolerance test (OGTT) to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT. A 2 hour value of equal to or over 11.1 mmol/L is diagnostic of diabetes.

Management:

- Diabetes UK suggests using the term 'prediabetes' when discussing the condition with patients as research has shown that this term has the most impact and is most easily understood and the term of impaired glucose regulation (IGR) when talking to other healthcare professionals.

- Lifestyle modification: weight loss, increased exercise, change in diet.
- Drug therapy is not currently licensed or recommended for patients with IGR in the UK.
- At least yearly follow-up with blood tests is recommended.

**EX:** Patient with **Fasting** glucose **6.6** mmol/l >> Impaired fasting glucose (**IFG**) >> **hepatic** insulin resistance.

#### **OGTT (Oral Glucose Tolerance Test):**

The OGTT has been used for many decades to diagnose diabetes. The test requires:

- **Overnight fast** prior to the test.
- Normal eating the previous day.
- **Baseline sample** for glucose using a fluoride tube.
- **75 g oral anhydrous glucose** usually washed down in **250-300 ml water** (if hydrous glucose is used, the same weight represents a lower proportion of glucose in molar measurement).
- Further glucose **sample taken at 120 minutes**.
- Plasma tubes, such as fluoride oxalate, must be used as the test results have not been validated using serum samples.
- Serum samples without additives allow further metabolism of the glucose by the red cells and may give a falsely low value. Fluoride oxalate prevents further metabolism of glucose.

The OGTT test has poor reproducibility but is particularly useful in cases of **borderline diabetes** or **gestational diabetes**.

#### **Glycosylated haemoglobin (HbA1c)**

Glycosylated haemoglobin (HbA1c) is the most widely used measure of long-term glycaemic control in diabetes mellitus.

HbA1c is produced by the glycosylation of haemoglobin at a rate proportional to the glucose concentration.

The level of HbA1c therefore is dependant on:

- 1) Red blood cell lifespan
- 2) Average blood glucose concentration

A number of conditions can interfere with accurate HbA1c interpretation:

<b>Lower-than-expected levels of HbA1c</b> (due to <b>reduced</b> RBCs lifespan)	<b>Higher-than-expected levels of HbA1c</b> (due to <b>increased</b> RBCs lifespan)
<ul style="list-style-type: none"> <li>➤ <u>Sickle-cell anaemia.</u></li> <li>➤ GP6D deficiency.</li> <li>➤ Hereditary spherocytosis.</li> <li>➤ Chronic liver disease.</li> <li>➤ Splenomegaly</li> <li>➤ Hypertriglyceridemia.</li> </ul>	<ul style="list-style-type: none"> <li>➤ Iron-deficiency anaemia.</li> <li>➤ Vitamin B12/folic acid def.</li> <li>➤ Alcohol dependence.</li> <li>➤ CRF</li> <li>➤ Hyperbilirubinaemia.</li> <li>➤ Splenectomy.</li> </ul>

HbA1c is generally thought to reflect the blood glucose over the **previous '2-3 months'**, although there is some evidence it is weighed more strongly to glucose levels of the past 2-4 weeks.

The relationship between HbA1c and average blood glucose is complex but has been studied by the Diabetes Control and Complications Trial (DCCT).

A new internationally standardised method for reporting HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC). This will report **HbA1c in mmol per mol of haemoglobin** without glucose attached.

<b>HbA1c (%)</b>	<b>Average plasma glucose (mmol/l)</b>	<b>IFCC-HbA1c (mmol/mol)</b>
5	5.5	
6	7.5	42
7	9.5	53
8	11.5	64
9	13.5	75
10	15.5	
11	17.5	
12	19.5	

**N.B:** From the above mentioned table we can see that:

**Average plasma glucose =  $(2 * \text{HbA1c}) - 4.5$**

**NB:** Compared with subjects with normoglycaemia, **beta cell mass** is **reduced**:

- By **50%** in subjects with **Impaired Fasting Glucose**,
- By **65%** in subjects with **Type 2** diabetes, and
- **Over 90%** in subjects with **type 1** diabetes.

The suggestion therefore is one of gradual insulin deficiency associated with increasing insulin resistance.

### **Diabetes mellitus: management of type 2**

NICE updated its guidance on the management of (T2DM):

#### **Dietary advice:**

- Encourage high fibre, low glycaemic index sources of carbohydrates.
- Include low-fat dairy products and oily fish.
- Control the intake of foods containing saturated fats and trans fatty acids.
- Limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake.
- **Discourage use of foods marketed specifically at people with diabetes.**
- Initial target weight loss in an overweight person is 5-10%.

#### **HbA1c:**

- The general target for patients is **48 mmol/mol** (DCCT = **6.5%**).
- HbA1c levels below 48 mmol/mol (DCCT = 6.5%) should not be pursued.
- However, individual targets should be agreed with patients to encourage motivation.
- HbA1c should be checked every 2-6 months until stable, then 6 monthly.

#### **Blood pressure:**

- Target BP in DM is **135/75 mmHg**: Target is < 140/80 mmHg or < 130/80 mmHg if end-organ damage is present.
- **ACEIs** or **ARBs** are first-line.



**The NICE treatment algorithm** has become much more complicated following the introduction of new therapies for type 2 diabetes.

- NICE still suggest a trial of lifestyle interventions first (many local protocols now recommend **starting metformin upon diagnosis**).
- Usually **metformin** is first-line, **followed by** a **sulfonylurea** if the HbA1c remains > 6.5%.
- Sulphonylureas can be used as first-line if the patient is not overweight, metformin is contraindicated or not tolerated, or a rapid response to therapy is required.
- The addition of either **sulphonylureas or insulin** at step two.
- It does not recommend use of older first generation sulphonylureas such as chlorpropamide or glibenclamide (Daonil®), instead recommending use of **newer** agents such as **gliclazide (Diamicron®)**, **glimepiride (Amaryl®)** or **glipizide (MiniDiab®)**.
- Glibenclamide (Daonil®) is long-acting SU and likely to increase the risk of hypoglycaemia and hence “funny turns”.
- Maximum daily dose of **Diamicron** is **160 mg**, **Amaryl** is **6 mg**.
- If the patient is at risk from hypoglycaemia (or the consequences of) (e.g. a driver) then a **DPP-4 inhibitor** or **thiazolidinedione (TZD)** should be considered rather than a sulfonylurea.
- If patient is intolerant to metformin >>> use TZD (Pioglitazone).
- **Meglitinides e.g. Repaglinide (Novonorm®)** (insulin secretagogues):
  - Like sulfonylureas they bind to an ATP-dependent K<sup>+</sup> (K<sub>ATP</sub>) channel on the cell membrane of pancreatic beta cells.
  - Should be considered for patients with an erratic lifestyle.
  - They are particularly useful for post-prandial hyperglycaemia. Patients take them shortly before meals.
  - Adverse effects include weight gain and hypoglycaemia (but less so than sulfonylureas).
- **If HbA1c > 7.5% then consider human insulin.**
- **Metformin treatment should be continued after starting insulin.**
- Exenatide should be used **only** when insulin would otherwise be started, or obesity is a problem (BMI > 35 kg/m<sup>2</sup>) and/or the need for high dose insulin is likely. Continue only if beneficial response occurs and is maintained (> 1.0 %

percentage point HbA1c reduction in 6 months and weight loss > 3% at 6 months).

- (I.e. **No**: exenatide plus insulin at the same regimen in T2DM. Exenatide should **only** be used in combination with metformin, a sulfonylurea or both).

### **Starting insulin:**

- **Usually commenced if HbA1c > 7.5%.**
- NICE recommend starting with human **NPH** insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need.
- The appropriate recommended starting dose for intermediate acting insulin is **0.2 U/kg** or **a flat dose of 10 U**.
- A **titration** schedule based on fasting glucose levels is then recommended, with **an increase of 2 U of insulin every 3 days** until fasting glucose is in the target range of 3.9-7.2 mmol/L.
- If the fasting plasma glucose is more than 10 mmol/L, then a more aggressive uptitration schedule of 4 U every 3 days can be considered.
- **Insulin glargine (Lantus®)**: is a long acting insulin analogue, it is an amalgam of Glycine and Arginine: **Glycine** is at chain A position **A21** and **two Arginines** are added to B chain position **B30**.
- Glargine and Detemir are insulin analogues, as such they are considered by NICE to be **only** suitable in cases:
  - 1) Nocturnal hypoglycaemia is a problem on isophane (NPH) insulin
  - 2) Morning hyperglycaemia on isophane (NPH) insulin results in difficult day-time blood glucose control
  - 3) Rapid-acting insulin analogues are used for meal-time blood glucose control.

<p><b><u>EX</u></b>: the most appropriate initial insulin regime for young patient after being diagnosed with new onset Type1 DM &gt;&gt;&gt; <b>Meal time Actrapid and insulatard at night.</b></p>
--

### **Other risk factor modification:**

- Current NICE guidelines suggest giving aspirin to all patients > 50 years and to younger patients with other significant risk factors. However, recent evidence does not support this approach. The 2010 SIGN guidelines do not advocate the use of aspirin for primary prevention in diabetics.

- The management of blood lipids in T2DM has changed slightly. Previously, all patients with T2DM > 40-years-old were prescribed statins. Now, patients > 40-years-old who have no obvious cardiovascular risk (e.g. Non-smoker, not obese, normotensive etc.) and have a 10 years cardiovascular risk < 20% do not need to be given a statin.
- If serum cholesterol target not reach consider increasing simvastatin to 80mg once daily.
- If target still not reached consider using a more effective statin (e.g. Atorvastatin) or adding ezetimibe.
- Target total cholesterol is  $\leq 4.0$  mmol/l
- High **triglycerides** and **HDL**-cholesterol are the commonest lipid abnormality seen in **type 2 DM**, and both are associated **with increased cardiovascular risk**.
- In total, **triglycerides above 1.7** are thought to be **associated with a 30% increase in relative cardiovascular risk**.

The **secondary** prevention: **target** of: total cholesterol to be **<4** mmol/L, **LDL** to be **<2.0** mmol/L and of **triglycerides** to the **1.7** mmol/L.

Cross-sectional studies across the **Caucasian** population have suggested that **triglyceride/HDL ratio** is **most predictive** of **insulin resistance**.

As such TG/HDL can be used to stratify both future risk of the development of CV disease and future risk of DM.

**Weight loss** and **exercise** training is seen to impact on TG/HDL ratio; **metformin** and **pioglitazone** which impact on insulin resistance both lead to modest decrease in TG and an increases in HDL in some patients.

### Metformin

Metformin is a **biguanide** used mainly in the treatment of type 2 DM.

It has a number of actions which improves glucose tolerance (see below).

It acts to improve insulin sensitivity through mechanisms that decrease hepatic gluconeogenesis and improved muscle glucose utilisation, thus some insulin must be produced for it to have an effect.

Unlike sulphonylureas it does not cause hypoglycaemia and weight gain and is therefore first-line, particularly if the patient is overweight.

Metformin is also used in polycystic ovarian syndrome (PCO) and non-alcoholic fatty liver disease (NASH).

**Mechanism of action:**

- 1) Increases insulin sensitivity (is an insulin sensitizer).
- 2) Decreases hepatic gluconeogenesis.
- 3) May also reduce gastrointestinal absorption of carbohydrates.

**Adverse effects:**

- 1) Gastrointestinal upsets are common (nausea, anorexia, **diarrhoea**), intolerable in 20%.
- 2) Reduced vitamin B12 absorption - rarely a clinical problem.
- 3) Lactic acidosis with severe liver disease or renal failure.

**High dose (> 2 gm daily)** interferes with enterohepatic circulation of the bile salts (**Bile salt malabsorption**) >> **diarrhoea**.

Long term treatment with metformin increases the risk of vitamin B12 deficiency. The possibility of **metformin-associated B12 deficiency** should be considered in patients on metformin who suffer cognitive impairment, peripheral neuropathy, SCD of the cord or anaemia.

**Contraindications:**

- It is contraindicated in subjects with **renal failure**, **hepatic failure** and **heart failure** due to the association with **lactic acidosis**.
- Chronic kidney disease (CKD): NICE recommend reviewing metformin if the creatinine is > 130 µmol/l and **stopping** metformin if creatinine > **150** µmol/l or the **eGFR** is less than **30** ml/min/1.73m<sup>2</sup>.
- Do **not** use during suspected episodes of tissue hypoxia (e.g. Recent MI, sepsis).
- In the BNF, metformin is listed as contraindicated within 6 weeks of MI.
- Alcohol abuse is a relative contraindication.
- Stop 2 days before general anaesthetic, restart when renal function normal.
- Stop prior to IV contrast e.g. angiography, restart when renal function normal.

**NB:** It is now increasingly recognised that lactic acidosis secondary to metformin is rare, although it remains important in the context of exams.

**NB:** Metformin is now sometimes used in pregnancy, for example in women with polycystic ovarian syndrome.

**NB:** Metformin may be continued (or initiated) with an eGFR less than 60 mL/min/1.73 m<sup>2</sup>, but renal function should be monitored closely (every 3-6 months). The drug should be **stopped once eGFR falls to less than 30 mL/min/1.73 m<sup>2</sup> (creatinine more than 150 µmol/L).**

**N.B:** Gastrointestinal side-effects are more likely to occur if metformin is not slowly titrated up. The BNF advises leaving at least 1 week before increasing the dose.

If the patient is intolerant to standard metformin, then **modified release preparations** should be tried.

**N.B:** The most appropriate prescription is:

R/ Metformin 500mg OD with food for 14 days, then metformin 500mg bid for 14 days then review.

### Sulfonylureas (SU)

Sulfonylureas are oral hypoglycaemic drugs used in the management of T2DM.

They work by **increasing pancreatic insulin secretion (insulin secretagogues)**; and hence are only effective if functional B-cells are present.

On a molecular level they bind to an ATP-dependent K<sup>+</sup> (K<sub>ATP</sub>) channel on the cell membrane of pancreatic beta cells.

Common adverse effects:

- 1) **Hypoglycaemic episodes** (more common with long acting preparations such as chlorpropamide)
- 2) **Weight gain.**

Rarer adverse effects:

- 1) SIADH (syndrome of inappropriate ADH secretion).
- 2) Bone marrow suppression.
- 3) Liver damage (cholestatic).
- 4) Photosensitivity
- 5) Peripheral neuropathy
- 6) Sulphonylureas are a class of drugs associated with increased risk of RBCs oxidation and the absence of G6PD leads to haemolytic anaemia.
- 7) **Sulfonylureas should be avoided in pregnancy and breast feeding.**

**EX:** A **62-year-old Caribbean** man with **new onset type 2 DM** presents to the ER. He has increasing **lethargy** and **tiredness** **since** starting a **sulphonylurea** a **few days earlier**.

On examination he has **jaundiced** sclerae, his BP is 135/72 mmHg, and pulse is 95. His mucous membranes look a little pale.

Lab: **Hb=10**, **Bilirubin = 80 µmol/L** (N <17), **Heinz bodies** in peripheral film.

The most likely diagnosis is **Glucose-6-phosphate dehydrogenase (G6PD) deficiency**.

### Thiazolidinediones (TZD)

Thiazolidinediones are a new class of agents used in the ttt of type 2 DM.

They are **PPAR-gamma receptor agonists** and reduce peripheral insulin resistance.

The **Peroxisome Proliferator-Activated Receptor Gamma** (PPAR-gamma receptor) is an intracellular nuclear receptor. Its natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function. i.e it is **activated** by **free fatty acids** and the **TZD** such as pioglitazone.

It is an **insulin sensitiser**. It upregulates genes for enzymes which deal with the metabolism of free fatty acids. These lead to **increased peripheral insulin sensitivity**, and improve glucose uptake.

Pioglitazone is not associated with hypoglycaemia.

It reduces HbA1c by between 1 and 1.3%.

Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

#### **Adverse effects:**

- 1) **Weight gain**.
- 2) **Fluid retention** (in around 10% of patients) - therefore **contraindicated in heart failure**. The risk of fluid retention **is increased if the patient also takes insulin**.
- 3) **Liver** impairment: monitor LFTs.
- 4) Recent studies have indicated an increased risk of **fractures** as it **decrease** bone mineral density.
- 5) **Bladder cancer**: recent studies have showed an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64).

NICE guidance on thiazolidinediones: Only continue if there is a reduction of > 0.5 percentage points in HbA1c in 6 months.

### **Diabetes Mellitus: GLP-1 and the new drugs**

A number of new drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of **glucagon-like peptide-1 (GLP-1)**, a **hormone** released by **the small intestine in response to an oral glucose load**.

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in (T2DM).

In normal physiology an **oral** glucose load results in a **greater release of insulin** than if the same load is given intravenously - this known as the “**incretin effect**”. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue or inhibiting its breakdown, is therefore the target of two recent classes of drug.

#### **Glucagon-like peptide-1 (GLP-1) mimetics (e.g. Exenatide or Liraglutide):**

- Increase insulin secretion
- Inhibit glucagon secretion by the liver
- It suppresses appetite and slow gastric emptying
- It does **not increase insulin sensitivity**
- licensed for use in T2DM
- Must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.
- Patient has no need to self-monitor his blood glucoses by glucometer.
- May be combined with metformin, a sulfonylurea or a thiazolidinedione.
- Typically results in weight loss.
- It is a good choice in patients who are significantly overweight.
- Major adverse effect is nausea and vomiting.

**NICE guidelines on the use of Exenatide / Liraglutide:**

- Should be used **only** when:
  - 1) Insulin would otherwise be started,
  - 2) Obesity is a problem (BMI > 35 kg/m<sup>2</sup>) and
  - 3) The need for high dose insulin is likely.
- Continue only if beneficial response occurs and is maintained (> 1.0 % percentage point HbA1c reduction and weight loss > 3% in 6 months).

The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide:

- Increased risk of **severe pancreatitis.**
- Increased risk of renal impairment.

**Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, Sitagliptin):**

- Oral preparation.
- Trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia.
- Do not cause weight gain.
- SE: GIT disturbance: nausea, flatulence, diarrhoea and constipation.

NICE guidelines on DPP-4 inhibitors:

- Continue DPP-4 inhibitor only if there is a reduction of > 0.5 percentage points in HbA1c in 6 months.
- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione.

**MODY (Type 1.5 DM) ☺**

Maturity-onset diabetes of the young (MODY) is characterised by the development of type 2 diabetes mellitus in patients < 25 years old.

It accounts for 1-2% of diabetes cases, and is an important diagnosis as the therapy may be different compared with T1DM and T2DM.

It is sometimes called **type 1.5 DM.**

It is typically inherited as an **autosomal dominant** condition (i.e. There is usually a strong family history).



Over 6 different genetic mutations have been identified as leading to MODY.

**Ketosis is not a feature at presentation.**

**TTT:** **One** third of patients require insulin therapy and around **one** third may be controlled with oral hypoglycaemic drugs.

**Sulphonylureas (SUs)** would be the initial drug of choice, because at least for the first few years, capacity to secrete insulin is preserved, and use of SUs restores insulin release, avoiding the need for insulin therapy.

<b>MODY &gt;&gt;&gt; Autosomal <u>D</u>ominant</b>
--

**MODY 1:**

- < 10%
- Due to defect in HNF-4 alpha gene (Hepatocyte Nuclear Factor).

**MODY 2:**

- 20% of cases.
- Due to a defect in the glucokinase gene.
- 90% of MODY 2 are controlled on diet therapy alone.

**MODY 3:**

- **60%** of cases (**most common**).
- Due to a defect in the HNF-1 alpha gene

<p><b><u>EX:</u></b> Male pt. 18 yrs. old with recurrent episodes of penile thrush with positive family history of T2DM, FBS checked twice 8.1 and 8.2 mmol/l with HbA1C 8.9% &gt;&gt;&gt; <b>MODY type 3 &gt;&gt;&gt; Initial ttt <b>Sulfonylureas</b>.</b></p>
--

**Diabetic ketoacidosis (DKA)**

Approximately **25%** of patients with **type 1 DM** will **first present in DKA** although often there are symptoms such as thirst, polyuria and weight loss which have been ignored.

The most common precipitating factors of diabetic ketoacidosis (DKA) are infection, missed insulin doses and myocardial infarction.

The **low insulin level** in DKA >> stimulate **lipolysis** >> production of ketone bodies,  $\beta$ -hydroxybutyrate and acetoacetate, which can be used as a metabolic fuel.

American Diabetes Association diagnostic criteria for DKA are as follows:

- 1) Blood glucose >13.8 mmol/l
- 2) PH < 7.30
- 3) Serum bicarbonate <18 mmol/l
- 4) Anion gap > 10
- 5) Ketonaemia

A **raised amylase** in the **absence** of frank pancreatitis is common in patients with DKA, indeed many patients complain of a degree of abdominal pain at the time of presentation. **No** specific management is required and amylase falls with rehydration and control of blood glucose.

Management:

- 1) **Fluid** replacement: most patients with DKA are deplete around 5-8 litres. Isotonic saline is used initially.
- 2) **Insulin**: an intravenous infusion should be started at 0.1 unit/kg/hour. Once blood glucose is < 15 mmol/l an infusion of 5% dextrose should be started.
- 3) Correction of **hypokalaemia**.
- 4) **LMWH** to prevent DVT.

**The typical fluid deficit associated with DKA is approximately: 6 litres**

Complications of DKA and its treatment:

- **Cerebral oedema**
- Thromboembolism
- ARDS
- Acute renal failure
- Gastric stasis

The mortality associated with DKA remains stubbornly around the **2-5%** since the 1970s specifically, mortality relates to **cerebral oedema**.

### Hyperosmolar Hyperglycaemic Non ketotic Coma (HHNC)

Hyperosmolar hyperglycaemic state (HHS) is confirmed by:

- Dehydration.
- Increased urine specific gravity
- Plasma Osmolality > 320 mosmol/kg.
- Hypernatraemia.
- Hyperglycaemia >30 mmol/L with pH >7.3, bicarbonate >15mmol/L.
- **No significant ketonenaemia** <3mmol/L (however, A trace of ketones may be found).
- This state occurs in **older type 2 diabetic patients**, some residual insulin production preventing the development of ketoacidosis, which occurs in type 1 diabetic patients more commonly.
- In general there is **still enough insulin** in patients with type 2 DM to suppress ketogenesis, but insufficient to prevent hyperglycaemia and the hepatic resistance to glucagon.
- The mortality risk is **10-20%**, with a strong predilection to **thrombotic** events.
- In general, it results in **osmotic fluid shift to the intravascular space.**
- TTT: **IV fluid (0.45% saline)** + IV Insulin firstly 0.15 IU/kg/hour is recommended as an initial guide then with **correction** of blood glucose at **rate 3 mmol/hr.**

### Diabetic Neuropathy

NICE updated it's guidance on the management of **diabetic neuropathy** in 2010:

- First-line: oral duloxetine (Cymbalta ®) or Oral amitriptyline (Tryptizole ®) if duloxetine is contraindicated.
- Second-line treatment:
  - If first-line treatment was with duloxetine, switch to amitriptyline or pregabalin (Lyrica®), or combine with pregabalin.
  - If first-line treatment was with amitriptyline, switch to or combine with pregabalin.
- Other options: pain management clinic, tramadol (if no other strong opioids), topical Lidocaine for localised pain if patients unable to take oral medication.

**Duloxetine** is the standard first line therapy recommended in NICE guidelines for the management of **peripheral neuropathy**. The starting dose is **60 mg daily** although this may be increased **up to 120 mg/day**. It **cannot** be used in patients with a history of **acute narrow angle glaucoma**.

**Amitriptyline** is an **alternative** option to duloxetine if it is contraindicated; a dose of 10-75 mg/day is recommended.

Amitriptyline SE: **urinary retention** so take care with old male with **BPH**, and again is contraindicated in **glaucoma**.

**Gabapentin** is used in the management of neuropathy, but more usually **pregabalin** is recommended either as a **second** line agent or in combination with amitriptyline.

If there is **renal impairment**, **pregabalin** is preferable over gabapentin.

Carbamazepine is not featured in the NICE guidelines for the management of peripheral neuropathy.

**Gastroparesis (delayed gastric emptying):** (in > 50% of Diabetics)

- Symptoms include erratic blood glucose control, early satiety, and indigestion, regurgitation, bloating and vomiting.
- May need **Isotope gastric motility scintigraphy scan** & Electrogastrography (reveals tachygastria).
- Management options include metoclopramide, domperidone or erythromycin (prokinetic agents) and small frequent meals.

**Diabetic amyotrophy:**

It is not uncommonly a presenting feature of diabetes (**T2DM**) in the **elderly**.

It is thought to be caused by the **occlusion** of the **vasa nervorum** of the proximal lumbar plexus and/or femoral nerve.

It affects the **lumbosacral plexus LMNL**.

It is often **associated with poor diabetic control**, and may improve with good control (although it often **self-resolves with time**).

The features are of an **asymmetrical** but **bilateral quadriceps wasting** and **weakness** with **diminished knee reflexes**.

It may also be associated with **marked weight loss**.

The **improved glycaemic control** is the most important initial therapeutic intervention. If not be achieved by oral antidiabetic medications so **Insulin** is the most appropriate next step.

**Transition to insulin therapy** is recommended because it is likely to improve the glycaemic control and may impact progression of neuropathy.

**Recovery** of diabetic amyotrophy **happens over 3-4 months, but only 50%** achieve **complete** recovery.

**EX:** Old male patient 70 years old with two month history of **weight loss** and **weakness**. He says that his symptoms started with **a severe pain**, affecting lower back and anterior thighs. It had a **burning** quality and was worse at **night**.

Examination of the lower limbs reveals a **bilateral weakness of knee extension**. He is **unable to rise from the squatting position**. There is **absence of the knee reflex** but the ankle reflexes are preserved and both plantars are flexor. There are no abnormalities on sensory examination.

EMG shows **multifocal denervation** in paraspinous & leg muscles.

May be associated with **postural hypotension** due to **diabetic autonomic neuropathy**. **TTT:** bed-head elevation, support stocking, adequate intake of NaCl, fludrocortisone starting dose 50 Mcg/day up to 400 Mcg/day, avoid diuretics, vasodilators, CCBs and TCA as they may exacerbate the condition.

D.D: Osteomalacia, hyperthyroidism and Cushing's would be unlikely as the proximal myopathy involves quadriceps and hamstrings and knee reflexes would be preserved. Pain is usually not a predominant feature.

D.D: Vitamin B12 deficiency tends to initially cause peripheral neuropathy, with loss of vibration sense and position followed by areflexia and weakness. This then develops into spasticity, Babinski plantars and ataxia if left untreated.

#### **Adhesive capsulitis (frozen shoulder):**

- limited **both active** and **passive** movements of **all** directions.
- The shoulder is **tender** to palpation.
- **Night** pain in the affected shoulder that may **interfere with sleep**.
- Pain and stiffness usually develop **gradually** over several months to a year but progress rapidly in some patients.
- It occurs more commonly in **women after age 50**.

- It is strongly associated with **DM type I** as many as **40%** of patients developing this problem at some stage.

**EX:** An 85-year-old woman with **DM** presented with **sudden onset** of **wild flinging movements** of the **left arm** which **disappeared during sleep**.

What is the most likely explanation >>> **hemiballismus**, and in diabetes is likely to be due to a **vascular event** in the **contralateral sub thalamic nucleus**.

TTT: Haloperidol or chlorpromazine or Topiramate.

#### **Diabetic foot ulceration (DFU):**

- The most common pathogens are aerobic Gram positive bacteria (particularly **Staphylococcus aureus** and beta-haemolytic Streptococci).
- **Callus formation at pressure areas** is an important predictor of potential ulceration.
- **Plantar** ulceration is usually a consequence of **neuropathy** and **minor skin trauma** is probably the most common initiating event.
- **Blood flow** is often **decreased** with autonomic neuropathy hence **sympathectomy** may be performed to improve skin blood flow.
- It is **difficult radiographically** to **distinguish** between Charcot's joint and osteomyelitis.

#### **Diabetic Retinopathy**

It is **the most common cause of blindness** in **adults aged 35-65 years-old**.

Diabetic retinopathy occurs in **both** type 1 and 2 DM and may be a presenting feature in type 2 as the **condition may have existed for many years prior** to diagnosis.

Progression may be slowed with **improved** both **glycaemic** and **hypertensive control** but the latter has been shown to be **more** effective at reducing progression (UKPDS).

There are no data at present to suggest that statin therapy reduces disease progression.

**Hyperglycaemia** is thought to cause increased retinal blood flow and abnormal metabolism in the retinal vessel walls. This precipitates damage to endothelial cells and pericytes.

Endothelial dysfunction leads to increased vascular permeability which causes the characteristic exudates seen on fundoscopy.

**Pericytes dysfunction** predisposes to the formation of **microaneurysms**.

**Neovascularization** is thought to be caused by the production of growth factors in response to retinal ischaemia.

**Despite** quite **marked** new vessel disease the **visual acuity may be normal**.

In exams you are most likely to be asked about the characteristic features of the various stages/types of diabetic retinopathy.

Recently a new classification system has been proposed, dividing patients into those with non-proliferative diabetic retinopathy (**NPDR**) and those with proliferative retinopathy (**PDR**):

Traditional classification	New classification
<p><b><u>Background retinopathy:</u></b></p> <ol style="list-style-type: none"> <li>1) <b>Microaneurysms</b> (MA) (dots)</li> <li>2) Blot haemorrhages (<math>\leq 3</math>)</li> <li>3) Hard exudates (HE): collections of exudated lipid and protein</li> <li>4) Seen in <b>both</b> type 1 &amp; 2 DM</li> </ol> <p><b><u>Pre-proliferative retinopathy:</u></b></p> <ol style="list-style-type: none"> <li>1) Cotton wool spots (CWS): (soft exudates; ischaemic infarcts of the nerve fibre layer of the retina)</li> <li>2) <math>&gt; 3</math> blot haemorrhages</li> <li>3) Venous beading/looping</li> <li>4) Deep/dark cluster haemorrhages</li> <li>5) More common in <b>Type I DM</b>, treat with <b>laser</b> photocoagulation.</li> </ol>	<p><b><u>Mild NPDR:</u></b></p> <ul style="list-style-type: none"> <li>• 1 or more microaneurysm</li> </ul> <p><b><u>Moderate NPDR:</u></b></p> <ul style="list-style-type: none"> <li>• Microaneurysms</li> <li>• Blot haemorrhages</li> <li>• Hard exudates</li> <li>• Cotton wool spots,</li> <li>• Venous beading/looping and</li> <li>• Intraretinal microvascular abnormalities (IRMA) less severe than in severe NPDR</li> </ul> <p><b><u>Severe NPDR:</u></b></p> <ul style="list-style-type: none"> <li>• Blot haemorrhages and microaneurysms in 4 quadrants</li> <li>• Venous beading in at least 2 quadrants</li> <li>• IRMA in at least 1 quadrant</li> </ul>

Prevalence	Risk factors
<ul style="list-style-type: none"> <li>➤ 2-6% of background retinopathy.</li> <li>➤ 20-60% pre-proliferative retinopathy.</li> <li>➤ 70-75% of proliferative cases</li> </ul>	<ul style="list-style-type: none"> <li>➤ ↑HbA1C</li> <li>➤ Proteinuria.</li> <li>➤ Duration of DM</li> </ul>

**Proliferative retinopathy:**

- Retinal **neovascularisation** - may lead to vitreous haemorrhage
- Fibrous tissue forming anterior to retinal disc
- More common in **Type I DM**, 50% blind in 5 years
- **Normal visual acuity** is seen in **proliferative retinopathy**.
- **Urgent** referral to **ophthalmologist** for **panretinal photocoagulation**.

**Maculopathy:**

- Based on **location** rather than severity, **anything is potentially serious**
- **Hard exudates** and other 'background' changes on macula.
- Check visual acuity.
- More common in **Type II DM**.

**Microaneurysm** on **fluorescein angiography** is the **earliest** sign of **Diabetic Nephropathy**.

**Asymmetric DM Retinopathy** >>> suspect **ocular ischaemia** (**carotid artery disease**)

**In T1DM >> Urgent** referral to an ophthalmologist (seen within one week) is required if there is **proliferative** retinopathy or there is evidence of clinically significant **macular oedema** (**hard exudates** at the fovea).

**Screening:**

- **T1 DM:**
  - Newly diagnosed DM → after 5 years
  - From 5-10 years → annual
  - More than 10 years → 6 monthly
- **T2 DM:**
  - Annually



**Pregnancy: diabetes mellitus**

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. **It complicates around 1 in 40 pregnancies.**

**Risk factors for gestational diabetes:**

- BMI of > 30 kg/m<sup>2</sup>
- Previous macrosomic baby weighing 4.5 kg or above.
- Previous gestational diabetes
- First-degree relative with diabetes
- Ethnic origin (South Asian, black Caribbean and Middle Eastern)

**Screening for gestational diabetes:**

- The 2 hour 75 g oral glucose tolerance test (**OGTT**) is used to diagnose gestational diabetes definitively.
- If a women has had gestational diabetes previously an oral glucose tolerance test (**OGTT**) should be performed at 16-18 weeks and at 28 weeks if the first test is normal.
- Women with any of the other risk factors should be offered an OGTT at 24-28 weeks.
- Currently the same WHO diagnostic criteria are used as for non-pregnant patients.
- There is however increasing evidence that a lower threshold should be used as treating borderline patients improves both maternal and neonatal outcomes.

NICE issued guidelines on the management of DM in pregnancy in 2008:

**Management of pre-existing diabetes:**

- Weight loss for women with BMI of > 27 kg/m<sup>2</sup>
- Stop oral hypoglycaemic agents, apart from metformin, and commence insulin.
- Folic acid 5 mg/day from pre-conception to 12 weeks gestation.
- Detailed anomaly scan at 18-20 weeks including four-chamber view of the heart and outflow tracts.
- Tight glycaemic control reduces complication rates
- Treat retinopathy as can worsen during pregnancy

**Management of gestational diabetes:**

- The **most** will respond to changes in **diet** and **exercise** in around **80%** of women.
- Only 10-20% of women need oral hypoglycaemia agents or insulin therapy.
- Women with gestational diabetes should aim to keep fasting blood glucose below 6 mmol/L and one hour postprandial blood glucose below 7.8 mmol/L during pregnancy.
- Hypoglycaemic therapy should be considered for women in whom diet and exercise fails to maintain blood glucose targets during a period of 1-2 weeks and/or if there is any evidence of fetal macrosomia therapy should be initiated immediately.
- Oral hypoglycaemic agents (metformin or glibenclamide Daonil ®) or insulin injections are needed **if** blood glucose control is poor **or** this is any evidence of complications (e.g. macrosomia).
- There is increasing evidence that oral hypoglycaemic agents are both safe and give similar outcomes to insulin.
- There is insufficient evidence regarding long-acting insulin analogues (Lantus and levemir), so isophane insulin (NPH) therefore remains the first choice for long-acting insulin during pregnancy.
- Insulin aspart (Novorapid ®) and lispro are safe rapid-acting analogues.
- It is important to note **HbA1c** should **not** be routinely used to monitor glycaemic control in the 2nd and 3rd trimesters.
- Hypoglycaemic medication should be stopped following delivery.
- A fasting glucose should be checked at the 6 week postnatal check

<b>GDM &gt;&gt;&gt; firstly</b> manage with <b>low carbohydrate Diet and exercise</b> , 2 <sup>nd</sup> : Metformin, Daonil or insulin (Regular & NPH).
---

**Hyperlipidaemia: secondary causes****Causes of predominantly hypercholesterolemia:**

- 1) Nephrotic syndrome.
- 2) Hypothyroidism.
- 3) Cholestasis.

**Causes of predominantly hypertriglyceridaemia:**

- 1) **Obesity**
- 2) **Alcohol**
- 3) **Diabetes mellitus (types 1 and 2)**
- 4) **Liver disease**
- 5) **Chronic renal failure**
- 6) Drugs: **thiazides**, non-selective beta-blockers, unopposed oestrogen

**Remnant hyperlipidaemia (type III hyperlipidaemia)  
(Mixed hyperlipidaemia) (Dys-betalipoproteinaemia)**

**Overview:**

- Also known as Fredrickson **type III hyperlipidaemia**, broad-beta disease and **dysbetalipoproteinaemia**.
- Rare cause of **Mixed** hyperlipidaemia (**raised cholesterol** typically 8-12 mmol/l **and triglyceride levels** typically 5-20 mmol/l).
- **Normal Apo B concentration.**
- Associated with **APO-E2 homozygosity** and occurs with a frequency of **1:100**.
- Definitive diagnosis is by **lipoprotein electrophoresis** or **genotyping of Apo-protein E**.
- It is transmitted as **autosomal recessive trait** and usually requires a secondary exacerbating metabolic factor for expression of the phenotype.
- Therefore **secondary causes of hyperlipidaemia** such as **obesity**, **DM**, **hypothyroidism**, renal insufficiency, high-calorie, high-fat diet or **alcohol** are often encountered at time of diagnosis.
- High incidence of **early onset** of age (around **30** yrs. old) for **ischaemic heart disease** and **peripheral vascular disease**.
- Thought to be caused by impaired removal of intermediate density lipoprotein (IDL) from the circulation by the liver.

**Features:**

- 1) **Palmer xanthomas** (yellow-orange discoloration of palm skin creases)
- 2) **Tuberous xanthomas** (elbows and knees).

**Management:**

- Fibrates are first line treatment.
- TTT of the secondary causes.

**Familial Hypercholesterolaemia (FH)**

Familial hypercholesterolaemia (FH) is an **autosomal dominant** condition that is thought to affect around 1 in 500 people in USA and Western Europe.

It is defined in the **WHO** classification as a type **II A** hyperlipidaemia.

**Homozygotes** present with **very early** cardiovascular disease, even as early as the **second** decade of life.

**Heterozygotes** rarely present before the age of 30 (i.e. **above 30**).

FH is caused by mutations in the gene which encodes the LDL-receptor protein.

It is due to **(LDL) receptor deficiency**, so it results in high levels of LDL-cholesterol which, if untreated, may cause early CVD.

Homozygous familial hypercholesterolaemia is exceedingly rare - most patients die in their teenage years from a myocardial infarction.

Clinical diagnosis is now based on the **Simon Broome criteria**:

- In adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- For definite FH: **tendon xanthoma** in patients or 1st or 2nd degree relatives or DNA-based evidence of FH.
- For possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels.

**Management:**

- The use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD.
- Referral to a specialist lipid clinic is usually required.
- The maximum dose of potent statins are usually required.
- **First-degree relatives** have a **50% chance of having the disorder** and should therefore be offered **screening**. This includes children who should be screened by the age of 10 years if there is one affected parent.

- Statins should be discontinued in women 3 months before conception due to the risk of congenital defects.

**EX:** **Markedly raised triglycerides + Xanthoma + recurrent** episodes of **upper abdominal pain**, nausea and vomiting + Family history of abdominal pain >>> **Chylomicronaemia syndrome** >>> it is due to a circulating **inhibitor** of lipoprotein lipase (type 1c hyperlipidaemia). It typically presents with eruptive xanthoma and abdominal colic. Complications include **retinal vein occlusion**, **acute pancreatitis**, and steatosis and lipidaemia retinalis.

TTT: **Fibrates**.

### Hyperlipidaemia: management

In 2008 NICE issued guidelines on lipid modification.

Patients over the age of 40 years with type 2 diabetes mellitus should be started on a statin if they have any other risk factors for cardiovascular disease, such as smoking, hypertension or a 'high-risk' lipid profile.

A high-risk lipid profile may be defined as:

- Total cholesterol > 4.0 mmol/L, or
- LDL cholesterol > 2.0 mmol/L, or
- Triglycerides > 2 mmol/L

#### Normal values:

- TC < 5 mmol/l
- TG < 2 mmol/l
- LDL-C < 3 mmol/l
- HDL-C > 1 mmol/l

### Primary prevention:

A systematic strategy should be used to identify people aged 40-74 who are likely to be at **high risk of cardiovascular disease (CVD)**, defined as a **10-year risk of 20% or greater**.

NICE updated their lipid guidelines so that the following risk models are valid:

- Framingham 1991
- Joint British Society 2 (JBS2)
- QRISK
- ASSIGN (Scotland only)

The 1991 Framingham equations may still be used. It is however recommended that adjustments are made in the following situations:

- First-degree relative with a history of premature coronary heart disease (which is defined as < 55 years in males and < 65 years in females) - increase risk by 1.5 times if one relative affected or up to 2.0 times if more than one relative affected.

- Males of South Asian ethnicity - increase risk by 1.4 times.

Along with lifestyle changes drug treatment should be considered for patients with a 10-year CVD risk of 20% or greater:

- Simvastatin 40mg OD is the first line treatment.
- There is **no target level** for TC or LDL-C for **primary** prevention.
- Liver function tests should be checked at baseline, within 3 months and at 12 months but not again unless clinically indicated.

**EX:** A 10-year risk of  $\geq 20\%$  is used to identify patients who should be considered for lipid-lowering therapy. >> Simvastatin 40mg OD is the first line treatment in patients with a significant risk. With no target level for total cholesterol or LDL-cholesterol for primary prevention.

### **Secondary prevention:**

All patients with CVD should be taking a statin in the absence of any contraindication.

NICE recommend increasing simvastatin to 80mg if a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre is not attained.

**EX:** Pt. had a myocardial infarction 6 months ago presents for review. He should have target cholesterol levels to be:

- Total cholesterol of  $< 4$  mmol/l.
- LDL cholesterol of  $< 2$  mmol/l.
- TG  $< 1.7$  mmol/l

**EX:** Pt with **subclinical hypothyroidism** ( $\uparrow$ TSH with normal fT4) plus **dyslipidaemia** >>> the most appropriate treatment for this dyslipidaemia is **Thyroxine**.

Thyroid hormone is known to play a role in regulating the synthesis, metabolism, and mobilisation of lipids. It is recognised that **the lipid abnormalities tend to resolve following treatment with thyroxine**.

NB: **HDL**:

**Women** has naturally higher HDL compared to men due to estrogen ☺

**COCP** also increase HDL ☺

**Exercise** is effective in raising HDL levels ☺

**Mild to moderate alcohol consumption** is associated with increase in HDL

☺ استخدام الكحوليات بنسبة بسيطة الى متوسطة مفيد لدهون الدم

**DM** (even **diet controlled DM**) causes lowered HDL and raised TG, but the TC level may be normal ☹

### Characteristic Xanthomata in hyperlipidaemia

#### Palmar Xanthoma:

- **Remnant** hyperlipidaemia
- May less commonly be seen in familial hypercholesterolaemia.

#### Eruptive Xanthoma:

- It is due to high **triglycerides** level and presents as multiple red/yellow vesicles on the extensor surfaces e.g. elbows and knees.
- Familial **hypertriglyceridemia**.
- **Lipoprotein lipase deficiency**.

#### Tendon Xanthomas, tuberous xanthoma, xanthelasma:

- Familial hypercholesterolaemia
- Remnant hyperlipidaemia

**The most clinical consistent sign with isolated hypertriglyceridemia is Lipaemia retinalis** which is an association between **isolated hypertriglyceridemia** and a pale pink milky appearance to the retinal vessels or even to the retina itself.

Xanthelasma are also seen without lipid abnormalities.

Managements of xanthelasma:

- Surgical excision
- Topical trichloroacetic acid
- Laser therapy
- Electrodesiccation

### Metabolic syndrome

Unfortunately there are a number of competing definitions of the metabolic syndrome around at the present time.

It is thought that the key pathophysiological factor is insulin resistance.

Decisions on primary prevention of cardiovascular disease should be made using standard tools and are not dependant on whether a diagnosis of metabolic syndrome is made.

**(SIGN)** recommend using criteria similar to those from the American Heart Association. The similarity of the International Diabetes Federation criteria should be noted.

For a diagnosis of metabolic syndrome **at least 3 of the following** should be identified:

- 1) **Elevated waist circumference**: men > 102 cm, women > 88 cm.
- 2) **Elevated triglycerides**: > 1.7 mmol/L.
- 3) **Reduced HDL**: < 1.03 mmol/L in males and < 1.29 mmol/L in females.
- 4) **Raised blood pressure**: > 130/85 mmHg, or active ttt of hypertension.
- 5) **Raised fasting plasma glucose** > 5.6 mmol/L (110 mg/dl), or previously diagnosed T2DM.

NECP ATP IIIM	Male	Female
Waist circumference	≥ 102 cm	≥ 88 cm
Blood pressure	≥ 130/85 mmHg	≥ 130/85 mmHg
HDL	≤1.03 mmol/L	≤1.29 mmol/L
	≤40 mg/dL	≤ 50 mg/dL
Triglyceride	≥ 1.7 mmol/L	≥ 1.7 mmol/L
	≥ 150 mg/dL	≥ 150 mg/dL
Fasting glucose	≥ 6.1 mmol/L	≥ 6.1 mmol/L
	≥ 110 mg/dL	≥ 110 mg/dL



The International Diabetes Federation (**IDF**) produced a consensus set of diagnostic criteria in 2005, which are now widely in use. These require the presence of **central obesity** (defined as waist circumference > 94cm for European men and > 80cm for European women, with ethnicity specific values for other groups) **plus any two of the following four factors**:

- 1) Raised **triglycerides** level: > 1.7 mmol/L, or specific treatment for this lipid abnormality
- 2) Reduced **HDL** cholesterol: < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality
- 3) Raised **blood pressure**: > 130/85 mm Hg, or active treatment of hypertension
- 4) Raised **fasting plasma glucose** > 5.6 mmol/L, or previously diagnosed type 2 diabetes

In 1999 the World Health Organization (**WHO**) produced diagnostic criteria which required the presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following:

- **Blood pressure**: > 140/90 mmHg.
- Dyslipidaemia: **triglycerides**: > 1.695 mmol/L and/or high-density lipoprotein cholesterol (**HDL-C**) < 0.9 mmol/L (male), < 1.0 mmol/L (female).
- **Central obesity**: waist: hip ratio > 0.90 (male), > 0.85 (female), and/or body mass index > 30 kg/m<sup>2</sup>.
- **Microalbuminuria**: urinary albumin excretion ratio > 20 mg/min or albumin: creatinine ratio > 30 mg/g.

**Other associated features include:**

- Raised uric acid levels
- NASH: Non-alcoholic fatty liver disease
- PCOD: Polycystic ovarian syndrome

**NB:** High LDL levels are not part of the International Diabetes Federation or the World Health Organization diagnostic criteria.

## Obesity

### Obesity physiology:

#### Leptin:

- It is thought to play a key role in the regulation of body weight.
- It is **produced (synthesized)** by **adipose tissue** and **acts on** satiety centers in the **hypothalamus** to ↓ appetite (i.e. **Leptin induces satiety**).
- More adipose tissue (e.g. in obesity) results in high leptin levels.
- Leptin plasma concentrations are **directly** related to **adipocyte (fat) mass** (NOT lean body mass).
- As such when patients reach a certain peripheral fat mass, leptin acts as a **lipostat** to **reduce food intake**.
- Leptin stimulates the release of melanocytes stimulating hormones (**MSH**) and corticotrophin-releasing hormone (**CRH**).
- Low levels of leptin stimulates the release of neuropeptide Y (NPY).

#### Ghrelin:

- **Ghrelin stimulates hunger.**
- It is produced mainly by the fundus of the stomach and pancreas.
- Ghrelin levels ↑ before meals and ↓ after meals.

#### **Obesity hormones:**

- 1) Leptin: ↓ appetite
- 2) Ghrelin: ↑ appetite
- 3) Thyroxine: ↑ appetite but not in obese pt.

#### **In obese person >>Obesity hormones & appetite:**

- **Leptin Lowers** appetite
- **Ghrelin Gains** appetite

### Glycaemic Index (GI):

- It describes the capacity of a food to raise blood glucose in normal glucose tolerant individuals.
- Foods with a high GI may be associated with ↑ risk of obesity and the post prandial hyperglycaemia, with such foods may also ↑ the risk of T2DM.

<b>High GI</b>	Straight glucose (100), <b>white rice (87)</b> , <b>baked potato(85)</b> , <b>white bread (70)</b> , corn flakes, rice, krispies, watermelon, croissants, extruded breakfast cereals.
<b>Medium GI</b>	Couscous (65), boiled new potato (62), digestive biscuits (59), basmati rice (58), whole wheat products, sweet potato, table sugar, most white rice (e.g. jasmine).
<b>Low GI</b>	<b>Fruits</b> and <b>vegetables</b> (except potatoes, watermelon), <b>peanuts</b> , grainy breads, pasta, legumes/pulses, milk, products extremely low in carbohydrates (fish eggs, meat, some cheese, nuts, cooking oil), brown rice.

**BMI:**

		<b>BMI (Kg/m<sup>2</sup>)</b>
1	Normal	18 – 25
2	Overweight	25 – 30
3	Obesity I	30 – 35
4	Obesity II	35 – 40
5	Obesity III (Morbid Obesity)	> 40

The management of obesity consists of a step-wise approach:

- 1) Conservative: diet, exercise
- 2) Medical
- 3) Surgical

The **average daily energy consumption** of a **male** is **2500** kcal and **2000** kcal for a **female**.

A guide to deciding the initial level of intervention to discuss				
BMI classification	Waist circumference			Co-morbidities present
	Low	High	Very high	
Overweight				
Obesity I				
Obesity II				
Obesity III				

☐ General advice on healthy weight and lifestyle.  
☐ Diet and physical activity.  
☐ Diet and physical activity; consider drugs.  
☐ Diet and physical activity; consider drugs; consider surgery.

Endocrinal causes of weight gain: **Cushing's** syndrome, **PCO**, **Hypothyroidism** and **Hypothalamic** disease (brain trauma or neoplasia).

#### Medical treatments of obesity:

##### Orlistat:

- Orlistat is a **pancreatic lipase inhibitor** used in the management of obesity.
- Adverse effects include faecal urgency/incontinence and flatulence.
- A lower dose version is now available without prescription ('Alli').
- **NICE** have defined criteria for the use of Orlistat. It should only be prescribed as part of an overall plan for managing obesity in adults who have:
  - 1) BMI of **> 30** kg/m<sup>2</sup> who has tried at least **3** months of diet and life style modifications, or
  - 2) BMI of **> 28** kg/m<sup>2</sup> **with** associated **risk factors (as DM, HTN, IHD, OSA)**, or
  - 3) Continued weight loss e.g. at least 5% at 3 months.
  - 4) Orlistat is normally used for < 1 year.

If patients fail to lose at least 5% of their bodyweight within 3 months, orlistat should be discontinued.

##### Sibutramine:

- Withdrawn January 2010 by the European Medicines Agency due to an increased risk of cardiovascular events.
- **Centrally acting appetite suppressant** (inhibits uptake of serotonin and noradrenaline at hypothalamic sites that regular food intake).

- Adverse effects include hypertension (monitor BP and pulse during treatment), constipation, headache, dry mouth, insomnia and anorexia.
- Contraindicated in psychiatric illness, hypertension, IHD, stroke, arrhythmias.

### Rimonabant:

- A specific CB1 cannabinoid receptor antagonist, was withdrawn in October 2008 after the European Medicines Agency warned of serious psychiatric problems including suicide.

### NB:

- Combination ttt with anti-obesity drugs is not recommended.
- It should never be used as the sole element of treatment.
- Anti-obesity drug treatment should also be **discontinued** if weight loss is less than 5% after the first 3 months.
- Anti-obesity drug treatment should be **discontinued** if the individual regains weight at any time whilst receiving drug treatment.
- Diet and exercise have been shown to be **ineffective** over the long term.
- More than 90% of people who attempt to lose weight gain it all back.

### Obesity: bariatric surgery

The use of bariatric surgery in the management of obesity has developed significantly over the past decade.

It is now recognised that for many obese patients who fail to lose weight with lifestyle and drug interventions the risks and expense of long-term obesity outweigh those of surgery.

### **NICE guidelines on bariatric surgery for adults:**

Consider surgery for people with severe obesity if:

- They have a BMI of **40** kg/m<sup>2</sup> or more, or
- Between **35** kg/m<sup>2</sup> and 40 kg/m<sup>2</sup> and other significant disease (for example, type 2 DM, and HTN) that could be improved if they lost weight.
- All appropriate non-surgical measures have failed to achieve or maintain adequate clinically beneficial weight loss for at least 6 months.
- They are receiving or will receive intensive specialist management.

- They are generally fit for anaesthesia and surgery.
- They commit to the need for long-term follow-up.
- Consider surgery as a first-line option for adults with a BMI of more than 50 kg/m<sup>2</sup> in whom surgical intervention is considered appropriate.
- Consider Orlistat before surgery if the waiting time is long.

**Obesity >>> NICE bariatric referral cut-offs:**

- With risk factors (T2DM, HTN etc.): > 35 kg/m<sup>2</sup>.
- No risk factors: > 40 kg/m<sup>2</sup>.

Types of bariatric surgery:

- **Primarily restrictive**: laparoscopic-adjustable gastric banding (LAGB) or sleeve gastrectomy (SG).
- **Primarily malabsorptive**: classic biliopancreatic diversion (BPD) has now largely been replaced by bilio-pancreatic diversion with duodenal switch.
- **Mixed**: Roux-en-Y gastric bypass surgery.

Which operation?

- LAGB produces less weight loss than malabsorptive or mixed procedures but as it has fewer complications it is normally the first-line intervention in patients with a BMI of 30-39kg/m<sup>2</sup>.
- Patients with a BMI > 40 kg/m<sup>2</sup> may be considered for a gastric bypass or sleeve gastrectomy. The latter may be done as a sole procedure or as an initial procedure prior to bypass.
- Primarily malabsorptive procedures are usually reserved for very obese patients (e.g. BMI > 60 kg/m<sup>2</sup>)

Bilio-pancreatic diversion with duodenal switch >>> is a primarily malabsorptive procedure which reserved only for patients who are very obese (BMI > 60 kg/m<sup>2</sup>).

The **duodenum** is the primary site of absorption for both **iron** and **calcium**.

**All gastric bypass operations bypass the duodenum.**

Nearly all menstruating women will therefore require **iron supplementation**.

## **Hypoglycaemia**

Causes:

- Insulinoma - increased ratio of proinsulin to insulin.
- Self-administration (abuse) of insulin/sulphonylureas.
- Liver failure.
- Alcohol.
- Addison's disease.

Other possible causes in children:

- Nesidioblastosis - beta cell hyperplasia.

## **Insulinoma**

An insulinoma is a neuroendocrine tumour deriving mainly from pancreatic Islets of Langerhans cells ( $\beta$  cells).

### **Basics:**

- Most common pancreatic endocrine tumour (50%).
- Incidence 1-2/million/year.
- More common in females.
- 10% malignant, 10% multiple.
- Of patients with multiple tumours, 50% have MEN-1.

### **Features: (a one year history of weight gain and intermittent sweating)**

- Features of hypoglycaemia (e.g. feel hungry, sweaty, tremors, diplopia, weakness etc.): typically early in morning or just before meal.
- **Rapid weight gain** may be seen ( ~ 5 kg over the past 6 months)
- **High insulin**.
- **High C-peptide**.
- **Raised Proinsulin: insulin ratio.**

### **Diagnosis:**

- **Supervised, prolonged fasting** (up to 72 hours).
- CT pancreas: 90% of Insulinoma are less than 2 cm in size.

**Management:**

- Surgery.
- Diazoxide and somatostatin if patients are not candidates for surgery.

**EX.** A typical presentation of Insulinoma: A 47-year-old woman is referred to the general medical clinic. She has gained 10 kg in weight in the past 3 months but her main problem is episodic sweating and hunger. These episodes of sweating are associated with double vision and typically occur early in the morning. Clinical examination is unremarkable >>>? **Insulinoma** >>> She requires **confirmation** of the suspected diagnosis and this should be undertaken with a **72 hour fast**.

If the patient develops **symptoms** >>> then a **plasma glucose** is measured and if **low** >>> **Insulin** and **C-peptide** is then collected and the fast terminated.

**Measuring insulin and C-peptides with a normal glucose level** would provide **no meaningful** information. First we have to see whether she actually becomes hypoglycaemic.

**So if suspect Insulinoma >>> so firstly confirm by 72 hour fast.**

**NB:** Hyperinsulinaemia in the absence of raised C-peptide >>> highly suggestive of Insulin misuse.

**NB:** Elevation of both insulin and C-peptide may raise suspicion of sulphonylureas abuse >>> It is possible to assay urinary SU levels.

**Glucagon:**

Glucagon is designed to **increase provision of energy in a time of need**.

Glucagon **stimulates lipolysis**.

Glucagon leads to **stimulation of catecholamine** secretion.

It **delays gastric emptying** and **reduces pancreatic exocrine secretions**.

With respect to **glucose handling**, glucagon stimulates glycogenolysis, at the same time inhibiting glycolysis and activating gluconeogenesis >> **↑Glucose**.

Used in **severe hypoglycaemia** >> 1 mg (1 U) IM/SC/IV, repeat every 20 min once or twice.

Used in **βB** or **CCB toxicity** >>> IVI loading and maintenance dose.



### Glucagonoma

- Patient with **DM** with the **characteristic rash of Necrolytic Migratory Erythema (NME)**, therefore this diabetes may be secondary to a Glucagonoma.
- Glucagonoma is **extremely rare 1/20 million**.
- نادر جدا جدا ... واحد في كل 20 مليون
- Most primary tumours are **> 3 cm** in diameter, **70% are malignant** and more than **50% have metastasised** at the time of diagnosis.
- Diagnosis is confirmed by **raised plasma glucagon level**.
- Abdomen US or CT or Octreotide scanning for localization.
- TTT:
  - The potential for surgical cure is only 5%.
  - Octreotide is useful in controlling the rash.
  - Palliative chemotherapy.
  - TACE via hepatic artery

### DVLA: diabetes mellitus

Until recently people with diabetes who used insulin could not hold a HGV licence

The DVLA changed the rules in October 2011. The following standards need to be met (and also apply to patients using other OHG such as sulfonylureas):

- 1) There has **not been any episode of severe hypoglycaemic** event requiring the assistance of another person in **the previous 12 months**.
- 2) The driver has **full hypoglycaemic awareness**
- 3) The driver must show **evidence of adequate glycaemic control** by regular blood glucose monitoring\*, at least twice daily and at times relevant to driving.
- 4) The driver must demonstrate an **understanding of the risks of hypoglycaemia** and **the ability to manage hypoglycaemia independently**.
- 5) Here are no other debarring complications of diabetes.

From a practical point of view patients on insulin who want to apply for a Group 2 (HGV) (Heavy Goods Vehicles) licence need to complete a D2 form. They may will also be required to produce a D4 Medical examination report.

Other specific points for group 1 drivers:

- If on insulin then patient can drive a car as long as they have hypoglycaemic awareness, not more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months and no relevant visual impairment. Drivers are normally contacted by DVLA.
- If on tablets or exenatide no need to notify DVLA.

- If tablets may induce hypoglycaemia (e.g. sulfonylureas) then there must not have been more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months.
- If diet controlled alone then no requirement to inform DVLA.

\*to demonstrate adequate control, the Secretary of State's Honorary Medical Advisory Panel on Diabetes Mellitus has recommended that applicants will need to have used blood glucose meters with a memory function to measure and record blood glucose levels for at least 3 months prior to submitting their application.

Patients on insulin >>> may **now** hold a HGV licence if they meet strict DVLA criteria relating to hypoglycaemia i.e. **he can keep his HGV licence after discussion with the DVLA ☺**

### **Diabetes insipidus (DI) (= NO ADH)**

DI is a condition characterised by either a deficiency of antidiuretic hormone, ADH, (cranial DI) or an insensitivity to antidiuretic hormone (Nephrogenic DI).

This can be **confirmed** with a water deprivation test where failure of urine concentration would be expected.

#### **Causes of cranial DI:**

- 1) Idiopathic
- 2) Post head injury
- 3) Pituitary surgery as in TSS (Trans sphenoidal surgery).
- 4) Craniopharyngiomas.
- 5) Granulomatous disease such as Histiocytosis X, Tuberculosis, and Sarcoidosis could infiltrate hypothalamus or pituitary gland.
- 6) DIDMOAD is the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome).

#### **Causes of nephrogenic DI (NDI):**

- 1) Genetic:
  - The **more** common form affects the vasopressin (ADH) receptor (**V2 ADH receptor gene mutation**)
  - The **less** common form results from a **mutation** in the **gene** that **encodes** the **aquaporin 2 channel**.
  - Nephrogenic DI is usually **X linked recessive**.

- 2) Electrolytes: hypercalcaemia, hypokalaemia.
- 3) Drugs: Lithium and Demeclocycline (e.g. Doxycycline)
- 4) Tubulo-interstitial disease: post-obstructive uropathy, pyelonephritis, sickle-cell nephropathy, amyloidosis.

**Features:**

- Polyuria
- Polydipsia

**DD: Polyuria:**

- 1) DM
- 2) DI
- 3) Psychogenic polydipsia
- 4) Drug abuse (thiazide diuretic)

**Investigation:**

- 1) High plasma osmolarity ( $\uparrow$  Serum Na),
- 2) Low urine osmolarity
- 3) Water deprivation test: to confirm the diagnosis of DI.

Measuring **plasma and urine osmolality** is the **first** step in diagnosis of DI, when **inappropriately low urine osmolality** in the presence of a raised or normal (not low) plasma osmolality, this is suggestive of diagnosis of DI and **the water deprivation test** would be the obvious **next** step.

**Normal plasma osmolality = 270-300 mOsm/kg**

**Normal urinary osmolality = 350-1000 mOsm/kg**

**TTT:**

- Cranial DI >>> fluid replacement  $\pm$  Vasopressin (DDAVP) intranasal.
- Nephrogenic DI >>> Indomethacin and thiazide.

**Cranial DI post pituitary surgery** is very common, the most appropriate initial therapy is **match fluid output with appropriate adequate fluid replacement**, only some patients will require long term DDAVP replacement.

**EX:** Female patient with depression on lithium, she has dehydration, drowsiness, confusion, polyuria and increasing thirst, ↑ Serum Na 155 >>> **Nephrogenic DI.**

**EX:** A 24-year-old **female** presents with a 2 week history of **polyuria** and **polydipsia** together with frequent nocturia + **low Na** + **low K** + **High Ca** + **High glucose** + **High serum osmolality** >>> **Drug abuse (Thiazide)**

### Water deprivation test

Method:

- Prevent patient drinking water for **8 hours** or until 5% of body weight is lost.
- Ask patient to empty bladder.
- Hourly body weight.
- Plasma osmolality is measured every 4 hours.
- Urine osmolality and volume are measured every 2 hours.
- **Demopressin (DDAVP) 2mcg IM/SC** is given with urine volume & urine and serum osmolality are measured over the next 4 hours.

ime	Weight (kg)	Plasma osm	Urine osm	Urine vol (ml)
8 am	66.5	285	-	-
9 am	-	-	110	200
10 am	-	-	200	290
11 am	-	-	240	220
12 midday	66	300	290	200
1 pm	-	-	310	200
2 pm	-	-	320	202
3 pm	-	-	-	150
4 pm	65.2	304	340	156
DDAVP 1 microgram SC given at 4 pm and permitted to drink				
6 pm	66.4	290	810	15

**EX:** Case of cranial DI

- If serum osmolality rise above 305 mOsmol/kg, then the patient is said to have **DI** and the test is stopped.
- If urine osmolality < 300 mOsmol/kg after fluid deprivation, rising to above 800 mOsmol/kg or more than 50% after desmopressin injection >>>**Cranial DI**.
- If urine osmolality < 300 mOsmol/kg after fluid deprivation, remaining at less than 300 mOsmol/kg or only slight increase in urine osmolality < 50% after desmopressin >>> **Nephrogenic DI**.
- If urine osmolality reaches level > 800 mOsmol/kg **without** desmopressin >>> **primary polydipsia**.
- If urine osmolality is intermediate 300-800 mOsmol/kg, and fails to rise above 800 after desmopressin >>> **partial DI** or polydipsia.

		Starting plasma osm.	Starting urine osm.	Urine osm. post-DDAVP
1	Normal	Normal (275- 300)	> 600	> 600
2	Psychogenic polydipsia	Low	> 400	> 400
3	Cranial DI	<u>High</u>	< 300	> 600
4	Nephrogenic DI	<u>High</u>	< 300	< 300
5	SIADH	Low	High	----

### Craniopharyngioma

It is a **slow-growing, calcified cystic tumour** arising from the remnants of the craniopharyngeal duct.

It compromises about 4.5% of all childhood tumours.

It is slightly more common in **males** than females.

The symptoms develop very slowly and usually become manifest once the tumour has attained a diameter of 3 cm.

The commonest presentation in young patients is **growth failure** and **delayed puberty**.

**CT brain:** **suprasellar calcified cyst** with the cyst content having the same density as the CSF (the calcification is more common in children than in adults).

TTT: **Surgery** ± postoperative radiotherapy.

**EX:** Male boy 14 years old with **short stature, delayed puberty**, with 6 months headache, CT brain: **suprasellar calcified cyst >>> Craniopharyngioma**.

### Hypokalaemia with/without hypertension

For exams it is useful to be able to classify the causes of hypokalaemia in to those associated with hypertension, and those which are not.

#### Hypokalaemia with hypertension:

- 1) Conn's syndrome (primary hyperaldosteronism)
- 2) Cushing's syndrome
- 3) Liddle's syndrome (pseudo-hyperaldosteronism)
- 4) 11-beta hydroxylase deficiency\*
- 5) Carbenoxolone, an anti-ulcer drug
- 6) Liquorice excess.
- 7) Familial glucocorticoid remediable aldosteronism (GRA)

**NB:** \*21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension. It is associated with precocious puberty in boys.

**Liddle's syndrome** is a rare autosomal dominant disorder that mimics hyperaldosteronism the so-called **pseudo-hyperaldosteronism**., that there is **low renin and low aldosterone** resulting in hypokalaemia and alkalosis associated with hypertension. It is thought to be caused by disordered Na channels in the distal tubules leading to increased reabsorption of sodium, so **serum Na is usually higher**. Treatment is with either **Amiloride** or **triamterene** (**NOT** Aldactone).

**Conn's syndrome:** **primary** hyperaldosteronism: **low** renin due to primarily **high** aldosterone, while

**Liddle's syndrome:** **pseudo** hyperaldosteronism: **low** renin and also **low** aldosterone

Both **liquorice** and **carbenoxolone** inhibit **11bHSD** (11 beta hydroxyl-steroid dehydrogenase) and produce **pseudo-hyperaldosteronism** with hypertension and hypokalaemia yet appropriately **low renin** and **low aldosterone** concentrations.

**11bHSD** is responsible for the conversion of cortisol to the inactive cortisone, preventing activation of the mineralocorticoid receptor by cortisol but permitting activation by aldosterone.

### **Primary hyperaldosteronism:**

It is associated with **High BP + high aldosterone, low renin, alkalosis, low potassium, low magnesium and normal/high sodium.**

An important differential diagnosis here is **renal artery stenosis (RAS).**

Causes of primary hyperaldosteronism include:

- 1) **Conn's** syndrome (Adrenal hyperplasia / adenoma) causes **over 50%**.
- 2) **Adrenal carcinoma** (rare).
- 3) **Glucocorticoid deficiency** - also called **glucocorticoid-remediable aldosteronism (GRA)**. Note that this is isolated glucocorticoid (cortisol) deficiency driving high ACTH levels and increased aldosterone production. Addison's disease is different as it involves both glucocorticoid and mineralocorticoid deficiencies.

**Screening** for hyperaldosteronism should be considered for:

- 1) **Hypertensive patients with hypokalaemia (not due to treatment),**
- 2) Those **with marked diuretic-induced hypokalaemia (<3.0)** and
- 3) Those **with refractory hypertension (failure to respond to  $\geq 3$  agents).**

Primary hyperaldosteronism was previously believed to account for less than 1% of hypertension, but recent studies have shown **a much higher prevalence (up to 12%)** and have demonstrated that most patients are normokalaemic.

Hypokalaemia in the presence of ACEI and thiazide use is highly suspicious of primary hyperaldosteronism.

Quite marked hypokalaemia ( $K = 3$  mmol/L), even in the presence of ACEI, is a further pointer to the diagnosis.

Primary hyperaldosteronism may therefore be **the most common potentially curable cause of hypertension**, and as such should always be considered.

The **investigation of choice** is the **renin/aldosterone ratio (RAR)**, which will help differentiate between **primary hyperaldosteronism** (high aldosterone and low

**rennin**) and **renovascular disease** as possible causes (**both** renin and aldosterone will be **high**).

**RAS** usually cause **secondary hyperaldosteronism**.

The renin/aldosterone ratio (RAR), together with cortisol, can be used to diagnose primary hyperaldosteronism when you would expect the **aldosterone to be high, renin low** and **normal cortisol**.

If renovascular disease is suspected, then angiography or MRA is a reasonable approach to investigation, but this may follow aldosterone/renin estimation.

The differential **size** on **renal ultrasound** raises the possibility of **renal artery stenosis (RAS)**, which would result in **elevated both renin and aldosterone levels**.

The **spot aldosterone: renin ratio greater than 800** raises the strong possibility that this man is suffering from hypor-reninaemic hyper-aldosteronism as in RAS.

Whilst addition of further anti-hypertensives may drive his BP closer to goal they are unlikely to be effective and **surgery** is the most appropriate intervention.

Patients ingesting large amounts of sodium, those with renal impairment, or those taking beta-blockers can have **false-positive results**.

Salt-restriction, ACEIs and ARBs, spironolactone and other diuretics can lead to **false-negative results**.

So you should check **plasma renin, aldosterone and cortisol level after washout of antihypertensives for 2 weeks**.

Alpha-blockers (Doxazosin) and CCBs (amlodipine) are the hypertensives of choice in patients undergoing renin/aldosterone ratio measurements.

**MRI / CT abdomen (Adrenals)** is the investigation that is likely to confirm the possibility of an adrenal adenoma.

TTT:

-Adrenal adenoma >>> **Resection**

-Adrenal hyperplasia >>> **Spironolactone** for many years.

-Glucocorticoid suppressible hyperaldosteronism >>> **Dexamethasone**.



**Familial glucocorticoid remediable aldosteronism (GRA):**

Familial GRA is an **autosomal dominant** condition where a mutation leads to **ACTH responsive aldosterone production** from the zona **fasciculata** rather than the zona glomerulosa.

It occurs because the regulatory portion of the 11b-OH gene binds to the aldosterone synthase gene.

The **resistant hypertension, hypokalaemia** and **strong family history** are all pointers to the underlying diagnosis.

EX: Young male + resistant HTN + low K + with F/H + **good BP response** after a trial of **hydrocortisone**.

من هو الشاب المريض بالضغط العالي زى أهله الغير مستجيب لادوية الضغط والذي يتحسن بالكورتيزون

Current UK guidelines with regard to **CKD recommend referral for further investigation of atherosclerotic renal artery stenosis (RAS)** when there is:

- 1) **Refractory HTN** (BP >150/90 mmHg despite **3** antihypertensive);
- 2) **Recurrent episodes of flash pulmonary oedema despite normal left ventricular function (LVF).**
- 3) **Rise of >20% serum creatinine or fall of GFR >15% over 12 months** with high clinical suspicion of widespread atherosclerosis, **or during the first 2 months after initiation with a ACEIs or ARBs.**

**Hypokalaemia without hypertension:**

- 1) Diuretics
- 2) GI loss (e.g. Diarrhoea, vomiting)
- 3) RTA (type 1 and 2\*\*)
- 4) Bartter's syndrome
- 5) Gitelman syndrome
- 6) (Thyrotoxic) hypokalaemic periodic paralysis

**NB:** \*\*Type 4 RTA renal tubular acidosis is associated with **hyperkalaemia** as there is a **hypo-reninaemic hypo-aldosteronism**, which may also be produced with diabetic nephropathy, hence hyperkalaemia and hyponatraemia is more typical.

**Bartter's syndrome** is an inherited cause (usually autosomal recessive) of **severe** hypokalaemia due to defective chloride absorption at the  $\text{Na}^+ \text{K}^+ 2\text{Cl}^-$  co-transporter in the ascending loop of Henle. It should be noted that it is associated with normotension. It usually presents in childhood with failure to thrive, but it can also present in adolescence with polyuria, nocturnal enuresis, polyuria, polydipsia and growth retardation, weakness, and nephrocalcinosis with renal stones are common. No hypomagnesaemia. Urinary Na, K and CL are raised.

TTT is aimed at preventing K wasting, for example with **spironolactone** and electrolyte supplements. **Indomethacin** is also effective, by inhibiting excess prostaglandin synthesis.

**EX:** A 16-year-old male presents with lethargy + low serum K (2.8 mmol/L) + renal stones, otherwise all are normal >>> Bartter's syndrome.

**EX:** A 14-year-old boy is being investigated for **nocturnal enuresis**.

His mother also reports that he is not doing well academically at school and that he is easily fatigued by physical exertion. BP is normal.

Lab: K = **3**,  $\text{HCO}_3^-$  = **35**,  $\uparrow$ 24hrs urinary K = **250** mmol/24 hr (25-100).

The diagnosis: **Bartter's** syndrome (hypokalaemic metabolic alkalosis with urinary potassium wasting).

**Gitelman's syndrome** is due to a defect in the thiazide-sensitive  $\text{Na}^+ \text{Cl}^-$  transporter in the distal convoluted tubule. It is associated with hypokalaemia and normotension or low normal BP. Also there is metabolic alkalosis, **hypomagnesaemia** and **hypocalciuria** (low urinary calcium/creatinine ratio). TTT: **K<sup>+</sup> and Mg<sup>++</sup> replacement**, if failed >>> **Spironolactone**.

	BP	Renin	Aldosterone
Conn's syndrome	<b>HTN</b>	$\downarrow$	$\uparrow$
Liddle's syndrome	<b>HTN</b>	$\downarrow$	$\downarrow$
RAS	<b>HTN</b>	$\uparrow$	$\uparrow$
Bartter's syndrome	Normal	$\uparrow$	$\uparrow$
Gitelman's syndrome	Normal	$\uparrow$	$\uparrow$

☺☺ **Little** minded people (**Liddle**) would have HTN, but **gentlemen** (**Gitelman**) would not develop HTN ☺☺

Bartter's syndrome is like Gitelman's in (hypokalaemia, metabolic alkalosis and normotension) but Bartter's is **more severe** and patients therefore present **earlier** in childhood with **profound hypokalaemia** and hypotension with constipation, growth failure, muscle cramps and weakness and  $\pm$  nephrocalcinosis in **early childhood**.

But in Gitelman's urinary calcium excretion is low, and this can also be used as a differentiator.

#### **Hyperkalaemia and hyponatraemia:**

- Acute hypoadrenalism
- Type IV 4 RTA
- Congestive cardiac failure, hepatic and renal failure.

**Hypokalaemia** and **hyponatraemia** >>> in **Hyperaldosteronism** either primary like Conn's disease or pseudo-hyperaldosteronism like: **Liddle's syndrome and others**.

#### **Adrenal gland**

$$\text{GFR} = \text{ACD}$$

- Zona **G**lomerulosa (outside): **Mineralocorticoids**, mainly Aldosterone
- Zona **F**asciculata (middle): **Glucocorticoids**, mainly Cortisol
- Zona **R**eticularis (inside): **Androgens**, mainly DHEA (Dehydroepiandrosterone)

#### **Primary hyperaldosteronism (Conn's syndrome)**

It accounts for up to 10% of all hypertensive patients.

It is the most prevalent form of secondary hypertension.

It is now recognised as a common secondary cause of hypertension.

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome.

As the name suggests, **aldosterone levels are high** so this **suppresses renin levels**.

However, recent studies have shown that **bilateral idiopathic adrenal hyperplasia** is the cause in up to 70% of cases.

Differentiating between the two is important as this determines treatment.

Adrenal carcinoma is an extremely rare cause of primary hyperaldosteronism.

**Bilateral idiopathic adrenal hyperplasia** is the most common cause of primary hyperaldosteronism.

**Consider testing patients with:**

- Stage 1 hypertension (>160-179/100-109 mmHg).
- Stage 2 hypertension (>180/110 mmHg).
- Drug resistant hypertension.
- Hypertension and spontaneous or diuretic-induced hypokalaemia.
- Hypertension with adrenal incidentaloma.
- Hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (less than 40-years-old).
- Hypertensive first-degree relatives of patients with primary hyperaldosteronism.

**Features: (↑ Aldosterone >>> Na absorption, excrete K and H):**

- 1) HTN
- 2) Hypokalaemia (e.g. muscle weakness)
- 3) Alkalosis
- 4) Hypernatremia

**Investigations:**

- High serum aldosterone
- Low serum renin
- HRCT or MRI abdomen
- Adrenal vein sampling

**Management:**

- Na restriction.
- Bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone.
- Adrenal adenoma: surgery.

## Corticosteroids

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular).

They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

<b><u>Minimal</u> glucocorticoid activity,  <u>Very high</u> mineralocorticoid activity,</b>	<b>Glucocorticoid activity,  <u>high</u> mineralocorticoid activity,</b>	<b><u>Predominant</u> glucocorticoid activity,  <u>low</u> mineralocorticoid activity</b>	<b><u>Very high</u> glucocorticoid activity,  <u>minimal</u> mineralocorticoid activity</b>
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betamethasone

This is clinically relevant as there are some situations where it is important to combine high glucocorticoid (anti-inflammatory) activity with minimal mineralocorticoid (fluid-retention) effects. A good example is the use of **dexamethasone** for patients **with raised intracranial pressure** secondary to **brain tumours**.

### Side-effects:

The side-effects of corticosteroids are numerous and represent the single greatest limitation on their usage. Side-effects are more common with systemic and prolonged therapy.

### Glucocorticoid side-effects:

- Endocrine: impaired glucose regulation, increased appetite/weight gain, hirsutism, and hyperlipidaemia.
- Cushing's syndrome: moon face, buffalo hump, striae.
- Musculoskeletal: **proximal myopathy**, **osteopenia** and **osteoporosis** rather than osteomalacia, **avascular necrosis** of the femoral head. (**Osteoporosis >>> which leads to Vertebral collapse**).

- Immunosuppression: increased susceptibility to severe infection, reactivation of tuberculosis.
- Psychiatric: insomnia, mania, depression, psychosis.
- Gastrointestinal: peptic ulceration, acute pancreatitis.
- Ophthalmic: glaucoma, cataracts.
- Suppression of growth in children.
- Intracranial hypertension

**Mineralocorticoid side-effects:**

- Fluid retention.
- Hypertension.

**Selected points on the use of corticosteroids:**

- **Patients on long-term steroids** should have their doses **doubled** during **intercurrent illness**.
- The BNF suggests **gradual withdrawal** of **systemic** corticosteroids if patients have: received **more than 40mg prednisolone daily** for **more than one week**, received more than 3 weeks treatment or recently received repeated courses.

Patients on long-term steroids should have their doses **doubled** during **intercurrent illness**.

**Proximal myopathy**, **easy bruising** and **thin skin** are clinical features that are **most suggestive of Cushing's syndrome**.

Otherwise, abdominal striae, buffalo hump, and acanthosis nigricans are all features of obesity.

**Corticosteroids** are recognised to **inhibit osteoblast activity** and **increase osteoblast apoptosis**. This is thought to be a more important component in bone loss with respect to **steroid induced osteoporosis** versus any effect on osteoclasts.

Patients taking **7.5 mg or more of prednisolone daily for 3 months or longer** should be offered **osteoprotection**.

The most appropriate therapy advocated by the National Osteoporosis Society for the **prevention of steroid-induced osteoporosis** would be **bisphosphonate** therapy such as Didronel or alendronate.

These are the **only class** of drug shown to offer osteoprotection with steroid therapy.

**EX:** 26-year-old male **body builder** + **azoospermia** + Lab: **low FSH** and **low LH** but with **normal testosterone**.

The most likely diagnosis is **steroid-induced hypogonadism**.

**Body builders** may be involved in the illicit use of **anabolic and androgenic steroids**. These results are consistent with ongoing use of androgens. The hypogonadism if persistent may be treated with human chorionic gonadotropin (HCG).

### Cushing's syndrome: causes

#### 1) ACTH dependent causes:

- 1) **Cushing's disease (80%):** pituitary tumour secreting ACTH producing adrenal hyperplasia.
- 2) Ectopic ACTH production (5-10%): e.g. small cell lung cancer (SCLC).

**Cushing's disease (pituitary tumour)** is the most common, non-iatrogenic, cause of Cushing's syndrome.

TTT:

- 1) **Transphenoidal** hypophysectomy/adenomectomy: the **initial** treatment of choice.
- 2) **Laparoscopic adrenalectomy:** advised where pituitary surgery has failed.
- 3) **Ketoconazole** may be an effective treatment for patients **unfit for surgery and preoperatively**, it acts on several of P450 enzymes, including the first step in cortisol synthesis, cholesterol-side chain cleavage, and conversion of 11-deoxycortisol to cortisol. A **daily dose of 600-800 mg** often decrease cortisol production significantly and will help in controlling BP and blood sugar before moving to pituitary surgery.

The recurrence rate for Cushing's disease after surgery is of the order of 20-30% in most series and depends on the size of the tumour with macroadenomas having a higher rate of relapse.

4) **Metyrapone** inhibits 11-beta hydroxylase and as such **inhibits cortisol production**. It has a **relatively rapid onset of action** and as such may be of value **pre-operatively** in improving blood pressure and glycaemic control in patient with pituitary-dependent Cushing's without associated weight gain of other options such as insulin.

**Ectopic ACTH secretion** (e.g. secondary to **small cell lung cancer (SCLC)** which accounts for 50-75% of case of ectopic ACTH) is characteristically associated with very low potassium levels.

## **2) ACTH independent causes:**

- Iatrogenic: steroids
- Adrenal adenoma (5-10%)
- Adrenal carcinoma (rare)
- Carney complex: syndrome including cardiac myxoma.
- Micronodular adrenal dysplasia (very rare)

## **3) Pseudo-Cushing's:**

- Mimics Cushing's
- Often due to **alcohol** excess or severe depression
- Causes false positive overnight dexamethasone suppression test or false high 24 hr urinary free cortisol with increased 9 am and 12 am plasma cortisol.
- Insulin stress test may be used to differentiate.
- The mechanism of hormonal abnormality may be due to increased CRH secretion or impaired hepatic metabolism of cortisol.
- Hormonal abnormalities disappear rapidly during abstinence from alcohol.

**NB: Nelson's syndrome** occurs in approximately **30%** of patients **adrenalectomised** for Cushing's disease.

It is probably due to the clinical progression of the pre-existing pituitary adenoma after the restraint of hypercortisolism on ACTH secretion is removed.

Plasma **ACTH** levels are **markedly elevated**.

**Pituitary MRI** defines the extent of the tumour.

## **Cushing's syndrome: investigations**

Investigations are divided into **confirming** Cushing's syndrome and then **localising** the lesion.

A **hypokalaemic metabolic alkalosis** may be seen, along with impaired glucose tolerance.



An insulin stress test is used to differentiate between true Cushing's and pseudo-Cushing.

**Tests to confirm Cushing's syndrome:**

The two most commonly used tests are:

- 1) **Overnight dexamethasone suppression test(ODST)** (most sensitive)
- 2) 24 hrs urinary free cortisol (UFC).

The overnight dexamethasone suppression test is **the best test** to **diagnosis / screen** Cushing's syndrome.

There is some debate as to whether an Overnight dexamethasone suppression test or 24 hrs urinary free cortisol should be used to screen patients for Cushing's.

The 1 mg Overnight dexamethasone suppression test (ODST) has been shown to be more sensitive and is now much more commonly used in clinical practice.

UFC is often recommended and has a 95% specificity (85% specificity in the obese) and a 98% sensitivity.

If this is not offered then 24 hrs urinary free cortisol is the next best answer.

If the UFC is elevated, consider repeating it and consider the overnight or low-dose dexamethasone suppression tests.

The low dose dexamethasone suppression test is more reliable than the overnight test. If the cortisol is suppressed to less than 50 nmol/L, Cushing's syndrome is excluded.

**NB:** Dexamethasone is primarily metabolised by **Cytochrome p-450 system**, by **hepatic CYP3A4**, an enzyme complex responsible for the metabolism of many xenobiotics.

So **enzyme inducers** like smoking, alcohol, drugs as rifampicin, tegretol >>> induce CYP3A4 activity >>> **false positive ODST.**

**Overnight dexamethasone suppression test** = **1 mg** dexamethasone given at **11 pm** and the cortisol measured at 9 am the following morning. **A cortisol concentration less than 50 nmol/L** after this test would be regarded as **normal**.

**ODST >>> Failure to suppress cortisol below 50 nmol/L** on this test is **highly suggestive** of **Cushing's** with ~95% sensitivity and specificity.

**A 24 hour urine collection measuring free cortisol in the urine:** An **elevated cortisol** usually **above 250 nmol/day** suggests Cushing's syndrome.

**Random** cortisol or 9 am cortisol or ACTH provides **no** diagnostic information whatsoever.

High 24 hrs UFC+ low 9 am ACTH + adrenal mass by CT >>> Functional adrenal adenoma secreting cortisol.

The High-dose dexamethasone suppression test is used to help differentiate the cause of Cushing's syndrome

### **Localisation tests (3):**

The first-line localisation is **9am** and **midnight** plasma **ACTH (and cortisol) levels**.

If ACTH is suppressed then a non-ACTH dependent cause is likely such as an adrenal adenoma.

#### **1) High-dose dexamethasone suppression test:**

- If pituitary source then cortisol suppressed.
- If ectopic/adrenal then no change in cortisol.

#### **2) CRH stimulation:**

- If pituitary source then cortisol rises.
- If ectopic/adrenal then no change in cortisol.

**3) Inferior Petrosal sinus sampling of ACTH:** it is s an **extremely sensitive, specific** and **accurate** test for **differentiate** between **pituitary** and **ectopic ACTH** secretion. It samples venous blood draining from the pituitary gland, using a **femoral approach**. A raised ACTH from here compared to the periphery suggests a pituitary cause.

**The high-dose dexamethasone suppression test** can differentiate between the two forms of Cushing's syndrome (pituitary or ectopic source of ACTH), but is not as accurate as inferior petrosal sinus sampling.

The 8 mg overnight dexamethasone suppression test and 48 hour high-dose dexamethasone test are useful when baseline ACTH levels are equivocal. They can be very useful in determining whether a patient has pituitary or ectopic ACTH production. Greater than 90% reduction in basal urinary free cortisol levels supports the diagnosis of a pituitary adenoma; ectopic ACTH causes lesser degrees of suppression.

**Low dose dexamethasone test:** (48 hrs **0.5 mg** qds): (cortisol should fall below 50 nmol/L).

**High dose dexamethasone test** (48 hrs **2 mg** qds): the cortisol should suppress to 50% of the level found after low dose dexamethasone in cases of pituitary dependent CS.

### Addison's disease

**Autoimmune destruction** of the adrenal glands (**Autoimmune adrenalitis**) is the commonest cause of hypoadrenalism in the UK, accounting for **80%** of cases.

**21 Hydroxylase** is the enzyme involved in the cholesterol steroid pathway and has been found to be present in approximately 80% of cases.

**Anti-21 hydroxylase antibody** is typically found in auto-immune adrenalitis (Addison's disease).

**Addison's disease** (autoimmune hypoadrenalism) is associated with other endocrine deficiencies in approximately 10% of patients.

Hyponatraemia and a high potassium in a patient with lethargy is highly suggestive of Addison's disease. >>> Steroids should be given as soon as possible.

### Features:

- Lethargy, weakness, anorexia, nausea & vomiting, weight loss.
- Hyperpigmentation (especially palmar creases), vitaligo, loss of pubic hair in women (due to DHEA deficiency).
- Crisis: collapse, shock, pyrexia.
- Hypo-tension, hypo-glycaemia, hypo-natremia.
- Hyper-kalemia.
- Hyper-Renin and Hypo-Aldosterone.
- Metabolic acidosis. (Hypo PH)
- Macrocytic (pernicious) anaemia may occur
- Blood: Eosinophilia, lymphocytosis & Neutropenia.
- Slight elevation of TSH.
- Mild hypercalcaemia.

#### Addison's disease:

##### 5 Hypo:

- 1) Hypo-tension
- 2) Hypo-glycaemia
- 3) Hypo-natremia
- 4) Hypo-PH (MA)
- 5) Hypo-aldosterone

##### 2 Hyper:

- 1) Hyper-kalemia
- 2) Hyper-renin

The **most common** cause of adrenal insufficiency is **autoimmune adrenalitis**.

**Other causes of hypoadrenalism:**

**1) Primary causes:**

- Tuberculosis.
- Metastases (from e.g. bronchial, breast, kidney).
- Antiphospholipid syndrome (Hughes' syndrome).
- Meningococcal septicaemia (Waterhouse-Friderichsen syndrome).
- HIV: secondary to CMV-adrenalitis which is an immune reconstitution syndrome.
- Severe illness.

**2) Secondary causes:**

- Pituitary disorders (e.g. tumours, irradiation, and infiltration).
- Drugs: ACEI, Heparin, Lead poisoning.

**3) Exogenous glucocorticoids therapy.**

**4) Pseudo-hypoaldosteronism:** due to primary aldosterone resistance (rare, but may occur due to spironolactone).

The two causes of Addison's in immunocompromised patient is **HIV (CMV-Adrenalitis)** and **TB**.

**Investigations (3):**

1) The definite investigation is **ACTH stimulation test (Short Synacthen test):**

Plasma cortisol is measured before and **30 minutes** after giving Synacthen **250ug IM** (Normal response to **increase** cortisol **greater than 550 nmol/L**), if below than this so this is inadequate response to synacthen and there is adrenal insufficiency.

**Addison's disease.** >>> **Short Synacthen test** >>> will show **failure** of **cortisol** secretion to **exceed 550 nmol/L after 30 minutes** following IM/SC administration of ACTH.

**2) Adrenal autoantibodies**, are present in **75% of cases**, such as **anti-21-hydroxylase Ab** may also be demonstrated.

**3) Also (9 am cortisol and ACTH test):** **low 9 am cortisol level and High ACTH concentration (> 80 ng/l)** is a very sensitive diagnostic test of Addison's disease.

**TTT:** Exogenous glucocorticoid therapy: **Hydrocortisone 100 mg IV TDS.**

**NB:** Usually TFTs are abnormal at the time of diagnosis of adrenal insufficiency (↑TSH and ↓T4)

**EX:** In diabetic patient with autoimmune **hypoadrenalism** plus **hypothyroidism**, you cannot commence thyroid hormone replacement at this stage as it may precipitate a rapid deterioration in his adrenal crisis.

It would be most important to **confirm the diagnosis** of adrenal insufficiency by short synacthen test, then commence **IV hydrocortisone** then **re-check the TFTs a few weeks later** after stabilising glucocorticoid replacement.

**EX:** Old patient with **severe hypoglycaemia** and **witnessed seizures** at ER. He is given **50 ml of 50% dextrose** and he slowly recovers over the next one hour. **A serum cortisol concentration later returns as 800 nmol/L (120-600).** >>> It is **Insulinoma** >>> to be confirmed by Prolonged 72 hour fast.

**The appropriate cortisol response during his hypoglycaemic episode (cortisol 800) excludes hypoadrenalism.**

**N.B:** Dehydroepiandrosterone (DHEA) is the most abundant circulating adrenal steroid. Adrenal glands are the main source of DHEA in females - loss of functioning adrenal tissue as in Addison's disease may result in symptoms secondary to androgen deficiency, such as loss of libido and slight loss of pubic hair. Research is ongoing as to whether routine replacement of DHEA is beneficial.

The **pigmentation**, which is due to **increased** adrenocorticotrophic hormone (↑**ACTH**) in hypoadrenalism, would **exclude pituitary** infarction as the cause of the hypoadrenalism.

**EX:** Female Pt. with history of **recurrent DVT** and **confirmed hypoadrenalism** (↓**NA**, ↑**K**, +ve short **Synacthen test**) >>> **Antiphospholipid syndrome**.

APL syndrome is associated with arterial and venous thrombosis and has a predilection for **the adrenal veins** causing **adrenal infarction** / **Hge** with consequent **hypoadrenalism**.

## SIADH (↑ADH)

**Criteria:**

- 1) Normal Renal, Normal Adrenal and Normal Thyroid.
- 2) Normal liver and Normal heart.
- 3) No recent use of diuretics.
- 4) Clinical euvolaemia
- 5) Hyponatraemia  $< 135$  mEq/l
- 6) Hypotonic plasma  $P_{osmo} < 270$  mOsm/Kg (N: 275 – 300 mOsmol/L).
- 7) Inappropriate  $\uparrow$  urine osmolality  $> 1000$  mOsm/Kg (N: 350-1000 mOsmol/L)
- 8) Urine Na  $> 20$  mEq/L (due to it is concentrated urine).

Thyroid function test should be checked in an elderly patient presenting with unexplained personality change or cognitive impairment and need to be normal in order to make the diagnosis of SIADH.

**Causes of SIADH:**

Category	Examples
Malignancy	<ul style="list-style-type: none"> <li>• <b>Small cell lung cancer (SCLC)</b></li> <li>• also: pancreas, prostate</li> </ul>
Neurological	<ul style="list-style-type: none"> <li>• Stroke</li> <li>• Subarachnoid haemorrhage</li> <li>• Subdural haemorrhage</li> <li>• Meningitis/encephalitis/abscess</li> <li>• Head injury and neurosurgery operation</li> </ul>
Infections	<ul style="list-style-type: none"> <li>• Tuberculosis</li> <li>• Pneumonia</li> </ul>

Category	Examples
Drugs	<ul style="list-style-type: none"> <li>• <b>Sulfonylureas</b></li> <li>• <b>SSRIs</b></li> <li>• <b>TCA</b></li> <li>• <b>Antipsychotics:</b> (Haloperidol, quetiapine , clozapine)</li> <li>• <b>Carbamazepine</b></li> <li>• <b>Thiazide</b></li> <li>• Vincristine</li> <li>• Cyclophosphamide</li> <li>• <b>Omeprazole</b></li> </ul>
Other causes	<ul style="list-style-type: none"> <li>• Positive end-expiratory pressure (PEEP)</li> <li>• <b>Porphyrias</b></li> </ul>

**Management:**

- 1) Treating the underlying **cause**.
- 2) Correction must be done **slowly** to **avoid** precipitating **central pontine myelinolysis (CPM)**.
- 3) **Fluid restriction** to less than 1 litre per day.
- 4) **ADH (vasopressin) V2 receptor antagonists** (Tolvaptan) have been developed.
- 5) **Demeclocycline**: reduces the responsiveness of the collecting tubule cells to ADH >> it will induce nephrogenic D.I.: reserved for more refractory cases.
- 6) **Hypertonic saline** in very severe cases e.g.fits.

**N.B: Other points to diagnose SIADH:**

- Maintained hypervolemia.
- Suppression of RAS (renin angiotensin system)
- No equal concentration of ANP (atrial natriuretic peptide)
- Normal serum creatinine.
- Normal acid base and K balance.
- ↓ BUN
- ↓ Uric acid
- ↓ Albumin

**Antidiuretic hormone (ADH)**

ADH is a (9) **nona-peptide** manufactured (synthesised) in the **supra-optic (SO)** and **paraventricular (PV) nuclei** of the **hypothalamus** and released (secreted) from the **posterior** pituitary.

It acts on the **collecting ducts** improving water permeability and hence water retention.

ADH binds to **V2 receptors** which are found on the peritubular surface of cells in the **distal convoluted tubule** and **medullary collecting duct**. This leads to **insertion of aquaporin-2 channels** into the luminal membrane, enhancing permeability to water.

It promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels.

There are multiple subtypes of aquaporin channels, some of which, such as aquaporin 3, are involved in passage of water through the skin.

**V1 receptors** are involved in mediating **platelet aggregation** and do not have a role in controlling water reabsorption.

Antidiuretic hormone (ADH) >>> site of action >>> collecting ducts

ADH is known to **increase platelet aggregation**, as such it may be considered **prothrombotic** at **high** dose.

ADH actually leads to **increased** factor **VIII 8** production, and as such may be of utility in **treating some patients with haemophilia A**.



ADH leads to uterine and GI **smooth muscle contraction** and indirectly leads to a reduction in coronary artery blood flow.

Carbamazepine as well as other agents such as thiazides and SSRIs may potentiate its release.

Ethanol usually inhibits release.

### Phaeochromocytoma

#### **Basics:**

- Phaeochromocytoma is a rare catecholamine secreting neuroendocrine tumour of the medulla of the adrenal glands (originating in the chromaffin cells), or extra adrenal chromaffin cells.
- It secretes excessive amounts of catecholamines, usually adrenaline if in the adrenal gland (not extra adrenal) and noradrenaline.
- About **10%** are familial and may be associated with:
  - MEN type II a and b,
  - Neurofibromatosis and
  - Von Hippel-Lindau syndrome.
- Bilateral in 10%
- Malignant in 10%
- Extra-adrenal in 10% : sometimes called **paragangliomas** (most common site = organ of Zuckerkandl, adjacent to the bifurcation of the aorta)

Adrenal glands are the only source of adrenaline in the body

**Pheochromocytoma >>>> rule of 10 (10% BM EF) (Bilateral, Malignant, Extra-adrenal, Familial)**

#### **Features (symptoms & Signs):**

- ↑ HR
- ↑ BP, including paroxysmal (sporadic, episodic) increase of BP which sometimes can be more difficult to detect.
- Orthostatic hypotension (↓ SBP ≥ 20 mmHg or ↓ DBP ≥ 10 mmHg on making the patient stand)
- Skin: hot flushes and ? pigmentation
- Diaphoresis
- Flank abdominal pain, vomiting
- Restless and anxiety often resembling that of a panic attack

- Localized amyloid deposits found microscopically.
- **Episodic paroxysmal headache** was present in **80%**. It was usually of rapid onset, bilateral, severe, and throbbing (vascular), and associated with nausea in about half of the cases.
- **Glycosuria** occurs **during** the attack in **30%** of cases.
- **Goiter** if **MEN 2**.

**EX:** A **young man** presented with **intermittent severe headaches** with **high BP** (190/110 mmHg) and **high HR** (112 bpm) with ↓ **Na** and ↓ **K** >>> **phaeochromocytoma** >>> **24 hour urinary collection of catecholamines**.

**EX:** A young male with a 3 months history of episodes of HTN, headache, dizziness, vague central abdominal discomfort, goiter and glycosuria >>> **Pheochromocytoma (MEN 2)**.

**NB:** Pheochromocytoma can also present with **severe hypotension** from **catecholamine-induced cardiomyopathy**.

**EX:** Female pt. 50 years old severely unwell at ER with 3-h history of **severe SOB**, **tachycardia**, **hypotension** BP 80/60 mmHg, **bilateral fine basal rales** up to mid lung zones, ECHO: severe **cardiomyopathy** with **EF 30%**, pt. admits to have **recurrent episodes of headache** over the past month, **CT abdomen** shows **intra-abdominal mass 5 cm** close to the origin of inferior mesenteric artery.

This is **Pheochromocytoma (extra-adrenal)** with **catecholamine-induced cardiomyopathy**

### Tests:

- 1) **Three 24 hr urinary collection of catecholamine (not VMA)**.
- 2) **CT/MRI adrenal glands**.
- 3) **MIBG scan** (<sup>131</sup> Iodine-labelled Meta-iodo-benzyl-guanidine): is used in cases where a tumour is confirmed biochemically but cannot be identified on CT or MRI scanning.

The 24 hrs urinary collection of catecholamines is preferred to that of vanillylmandelic acid as it has a higher sensitivity. Three 24 hrs collections are needed as some patients have intermittently raised levels.

### TTT:

- **Surgery** is the definitive management.
- The patient must first be stabilized with medical management:

- **A**lpha-blocker (e.g. phenoxybenzamine), given before a
- **B**eta-blocker (e.g. propranolol)

**PH**aeochromocytoma >>> give **PH**enoxybenzamine before beta-blockers

Unopposed beta blockade should not be used in the management of phaeochromocytoma because of the risk of paradoxical increases in BP.

**Phenoxybenzamine:**

-It is the most potent available alpha blocker and is the treatment of choice for pheochromocytoma. **Starting dose 10 mg BID up to maximum 20 mg QDS.**

-**Beta blockade** can be started around **3 days after** phenoxybenzamine.

**IV** phenoxybenzamine is commonly used for the 3 days prior to surgery to ensure complete alpha blockade.

**Management of phaeochromocytoma in pregnancy** is difficult with maternal and fetal mortality both approximately 50%.

The primary management goal is to prevent hypertensive crisis, which can be harmful to both mother and foetus.

**Alpha blockade** (phenoxybenzamine or Doxazosin) should be started as soon as the diagnosis is made, and should be given **for 10-14 days**.

**Surgery** is the **definitive** treatment for phaeochromocytoma. The timing remains challenging and controversial.

**Laparoscopic adrenalectomy** is indicated if tumour mass is **less than 7 cm**.

Vaginal delivery carries a higher mortality rate of 31%, compared to 19% with **C-section**. **General anaesthesia is recommended**.

The correct management in this situation is therefore to **initiate alpha-blockade** and **arrange delivery by C-section with GA**.

**Phaeochromocytoma in pregnancy >>> alpha-blocker + arrange delivery by C-section by GA + later surgery for the tumour.**

**NB:** Usually **medullary carcinoma of the thyroid (elevated serum calcitonin)** is associated with pheochromocytoma, so adrenal gland imaging is recommended in any patient with medullary carcinoma of the thyroid.

**NB:** DD of **FUO (Fever of unknown origin)** and **bilateral adrenal swelling** is: **TB, Lymphoma** or **Histoplasmosis**.

### Growth hormone (GH)

It is an **anabolic** hormone secreted by the **somatotroph** cells of the **anterior** lobe of the pituitary gland.

It has actions on **multiple** organ systems and is important in postnatal growth and development.

GH is also responsible for changes in protein, lipid, and carbohydrate **metabolism**.

Mechanism of action:

- Acts on a **transmembrane receptor** for growth
- Binding of GH to the receptor leads to receptor dimerization.
- Acts **directly** on tissues (e.g. stimulates division and multiplication of cartilage chondrocytes or bone osteoblasts) and **indirectly** via insulin like growth factor 1 (IGF-1), primarily secreted by the liver.

Conditions associated with GH disorders:

- Excess GH: acromegaly
- GH deficiency: resulting in short stature

The commonest side effect of recombinant human GH therapy is **fluid retention** so **may be associated** with **IIH (Idiopathic intracranial hypertension)**, though other side effects include: gynaecomastia, hypertension, and atrial fibrillation.

**IGF-1** are often **increased** in **Acromegaly** and **pregnancy**.

**Reduced** IGF-1 is typically found in:

- **Adult GHD**
- **Liver cirrhosis** due to reduced synthesis
- **CKD**
- **DM**, and
- **Starvation**.

### **Acromegaly**

In acromegaly there is excess growth hormone secondary to a pituitary adenoma in over 95% of cases.

A minority of cases are caused by ectopic GHRH or GH production by tumours e.g. pancreatic.

A significant percentage of GH secreting tumours are thought to have a **mutation** in the **alpha** sub-unit of the stimulatory guanosine triphosphate (**GTP**) binding protein >>> this leads to persistent **elevation of cyclic adenosine monophosphate (↑cAMP)** and hence production of excess growth hormone.

#### **Features:**

- Coarse facial appearance, spade-like hands, increase in shoe size.
- Large tongue, prognathism, interdental spaces.
- Excessive sweating and oily skin (The increased sweating is caused by **sweat gland hypertrophy**).
- Features of pituitary tumour: hypopituitarism, headaches, bitemporal hemianopia.
- Raised prolactin in 1/3 of cases → galactorrhoea.
- 6% of patients have MEN-1.
- Pseudogout is seen in acromegaly but not gout.
- Goitre is seen in 20%, along with other soft tissue swelling.
- Phosphate are elevated but calcium are not significantly increased.

#### **Complications:**

- 1) Hypertension.
- 2) Diabetes (>10%).
- 3) Cardiomyopathy.
- 4) Colorectal cancer.

N.B: Acromegaly is associated with systemic HTN rather than pulmonary HTN
---

**Investigations:**

- Growth hormone (GH) levels vary during the day and its release is pulsatile and so therefore not diagnostic.
- The definitive (diagnostic) test is the **oral glucose tolerance test (OGTT) with serial GH measurements.**
- **Elevated Serum IGF-1** (insulin-like growth factor 1): has a **long half-life**. It may also be used as a screening test and is sometimes used to monitor disease, but this is not diagnostic.
- A pituitary MRI may demonstrate a pituitary tumour.

**Oral glucose tolerance test (OGTT):**

- In normal person GH is suppressed to < 0.3 mcg/L with hyperglycaemia.
- In acromegaly there is **NO suppression of GH**, or paradoxical elevation
- May also demonstrate impaired glucose tolerance which is associated with acromegaly.

**Management:**

<b>Acromegaly &gt;&gt;&gt; TTT: Somatostatin analogue <u>followed by</u> trans-sphenoidal surgery.</b>
--

**1) Trans-sphenoidal surgery (TSS)** is first-line treatment for acromegaly in the majority of patients.

**2) Dopamine agonists:**

- For example Bromocriptine.
- The first effective medical treatment for acromegaly, however now superseded by somatostatin analogues.
- Effective only in a minority of patients
- It is only more useful for ttt pf prolactinomas rather than GH producing tumours.

**3) Somatostatin analogue:**

- For example Octreotide.
- Effective in 50-70% of patients.
- It is the **initial first medical therapy of choice.**
- May be used as an adjunct to surgery.

- It is useful in controlling cardio-metabolic risk factors prior to surgery.
- It is associated with tumour shrinkage and resolution of some clinical symptoms prior to progression to trans-sphenoidal surgery.

### 4) Pegvisomant:

- It is genetically modified analogue of human GH and is a **highly selective GH receptor antagonist** >> prevents dimerization of the GH receptor.
- Once daily S/C administration.
- Very effective as It has been shown to normalise insulin-like growth factor-I (IGF-I) levels in 90-100% of patients with a history of acromegaly.
- It is the usual **second** line of **medical** therapy.
- GH levels increase during treatment and **no decrease in tumour size** is seen, as such the major use of pegvisomant is in patients who have an **inadequate** response to surgery or radiotherapy.
- Doesn't reduce tumour volume therefore surgery still needed if mass effect.

5) External irradiation is sometimes used for older patients or following failed surgical/medical treatment.

If patient does **not wish** for **surgery** at present but agree to try **medical** therapy >>>> 1) **Octreotide**, then 2) **Pegvisomant**.

If treatment of acromegaly is unsuccessful, the **death rate** from cardiovascular, cerebrovascular, respiratory and malignant disease is **2 to 4 times** that of the general population.

Classically the **malignancy** associated with acromegaly is **tumour** of the **large intestine (cancer colon)**.

**Mortality** is typically due to a **cardiovascular** cause if the condition is untreated.

Thus **heart failure (LVH)** is probably more common a cause of death than colonic neoplasia.

**Growth hormone deficiency (GHD):**

Although **an insulin tolerance test** is the **gold** standard for the diagnosis of GHD, it is **contraindicated** due to the **epilepsy**.

A **peak GH response** of **less than 10 mU/L** to insulin-induced hypoglycaemia.

Therefore **GHRH/arginine** is regarded as a suitable alternative.

IGF-1 levels can be used as marker of growth hormone levels, but are not diagnostic. There are situations in which the IGF-1 level is normal even though there is GH deficiency so **a normal result of IGF-1 does not exclude GH deficiency**. In addition, decreased levels of IGF-1 can be seen with nutritional deficiencies, chronic kidney or liver disease and with high doses of oestrogen.

**Sheehan's syndrome** is post-delivery infarction of the pituitary and GHD is typical.

Patient with **pan-hypopituitarism with replacement** of thyroxine + hydrocortisone+ testosterone and has **tiredness** and **central weight gain** >>> so should think of **adult growth hormone deficiency (AGHD)** supported by the **low IGF-1** conc. >>> Recent evidence would suggest that **GH replacement therapy** in addition to his current replacement therapy does **improve** symptoms and **quality of life**.

Although GH therapy is used in CRF, Turner's syndrome and short stature subjects but they are not GH deficient.

NB: **Laron's syndrome** is due to a GH **receptor defect** with impaired IGF-1 production.

The gold standard test is the **insulin tolerance test**, where insulin is given to stimulate significant **hypoglycaemia** (glucose less than 2.2 mmol/l).

This provokes **GH** and adrenocorticotrophic hormone (**ACTH**) release.

Samples are taken at baseline and at 30, 60 and 90 minutes.

A normal result is a rise in cortisol to more than 550 nmol/L and a rise in GH to more than 10 µg/L.

Patients with a history of seizures or heart disease are unsuitable for this test.

A random GH level must be interpreted with caution due to significant diurnal variation.

A level of GH greater than 3 µg/L probably excludes GH deficiency.

Normal **GH** stimulates **IGF-1** release and IGF-1 concentrations are often low in GH deficiency.



**EX:** A 25-year-old woman comes a few weeks after the birth of her first child. Unfortunately she suffered a **postpartum haemorrhage** and required a three unit **blood transfusion**.

Over the past few weeks she has been feeling increasingly tired but puts this down to post pregnancy blues. She tells you that she seems to be losing her hair. O/E her **BP is 100/60 mmHg**, pulse is 62 and regular.

Lab: Hb 10, **↓Na 130**, **↑K 5.1**, **↓TSH 0.2**

The most likely diagnosis is **Sheehan's syndrome**

The clues here centre on the **postpartum haemorrhage**, **electrolyte disturbance**, and **low TSH**.

The **absence of pigmentation** in the presence of **electrolyte disturbance** consistent with **adrenal insufficiency** also helps point us towards **pituitary** disease (this is **pan hypopituitarism** leading to adrenal insufficiency, rather than Addison's).

**MRI of the pituitary** and pituitary function testing including **LH/FSH** are indicated.

DD: Hashimoto's and postpartum thyroiditis would not be associated with the electrolyte disturbance seen here.

### Pituitary apoplexy

**Sudden** enlargement of pituitary tumour **secondary** to haemorrhage or infarction. A pituitary adenoma usually pre-exists.

Endocrinologically, the main initial problem is a **lack of adrenocorticotrophic hormone (ACTH)**, which results in a lack of cortisol and the features of an '**Addisonian crisis**', i.e. hypotension, hyponatraemia, hyperkalaemia and hypoglycaemia. Subacutely, there can be deficiency in thyroid stimulating hormone (TSH) and gonadotropins (LH and FSH).

The mild hyponatraemia may be a consequence of the either SIADH or secondary hypoadrenalism.

Features:

- 1) **Sudden onset headache** similar to that seen in SAH.
- 2) **Vomiting**
- 3) **Neck stiffness**
- 4) **Visual field defects:** classically **bitemporal** superior quadrantic defect.

- 5) **Extra ocular** nerve palsies in up to **80%**, with **III** nerve palsy the commonest finding.
- 6) Features of pituitary insufficiency e.g. **Hypotension** secondary to **hypoadrenalism**.

The combination of **headache**, vomiting, **visual disturbance** and **hormonal** dysfunction should lead you to consider a diagnosis of pituitary apoplexy.

**MRT pituitary** to confirm the diagnosis

TTT: **Hydrocortisone IV** should be given to prevent Addisonian crisis.

**EX:** A 47-year-old man presents to the Emergency Department with a **3 day history of severe headache** associated with **vomiting**. There is no past medical history of note. On examination **BP is 98/62 mmHg**, pulse is 108 bpm and temperature is 37.0°C. There is **mild neck stiffness** and a **partial third nerve palsy of the left eye**. Blood tests reveal: **Na<sup>+</sup> = 130, K= 5.2, Low free T4**. The most likely diagnosis is >>> **Pituitary apoplexy**.

### Thyrotoxicosis

Causes:

- 1) **Graves' disease**: It accounts for 50-60% of cases of thyrotoxicosis
- 2) Toxic nodular goitre.
- 3) Toxic adenoma (Plummer's disease)
- 4) Subacute (de Quervain's) thyroiditis.
- 5) Acute phase of Hashimoto's thyroiditis (later results in hypothyroidism)
- 6) Post-partum thyroiditis.
- 7) Amiodarone therapy
- 8) Thyrotoxicosis factitia

Investigation:

- TSH down, T4 and T3 up
- Thyroid autoantibodies
- Other investigations are not routinely done but includes isotope scanning

**N.B:** In a Pt. is started on carbimazole 20mg bid following a diagnosis of Grave's disease. What is the best biochemical marker to assess her response to treatment? >>> **TSH**. There is however a significant proportion of patients for whom TSH monitoring alone is insufficient. TSH may remain suppressed for several weeks as

continued production of thyroid stimulating immunoglobulins seen in Grave's disease reduces the need for the pituitary to secrete TSH.

**Factitious hyperthyroidism** is **rare** and it is important to **exclude** other causes before jumping to this conclusion. You can measure the **serum thyroglobulin**, which is **low** in factitious hyperthyroidism.

It is inappropriate abuse of thyroid hormone, ↓TSH, ↑FT4 with **NO** goiter, and **decreased** isotope thyroid scanning.

TTT: Psychological advice.

**NB:** Isolated **T3 thyrotoxicosis** (↓TSH, ↑FT3 with normal T4) is about **5%** of cases of thyrotoxicosis. TTT: as usual.

The diagnosis of T3 thyrotoxicosis should be suspected in patients presenting with **symptoms of thyrotoxicosis** (including a goitre) in whom **serum T4 and fT4 are normal or low** with ↓ **TSH** and in whom the **RAIU is increased**.

**EX:** Pt with **thyrotoxicosis** with a diffuse goitre with **High level of all FT4, FT3 and TSH >>>** as the non-suppressed TSH suggests that this is due to **excessive TSH** production by the **pituitary** gland, the possibility of a **thyrotroph adenoma (TSH-oma)** must be pursued >>> **MRI pituitary**.

**Thyroid hormones: enhance all the following:**

- Insulin sensitivity (Insulin-dependent entry of glucose into cells)
- Myocardial oxygen consumption
- Nerve conduction
- Gluconeogenesis, and
- Oxidation of fatty acids.

**NB: Secondary hyperthyroidism** with **elevated Free T3, elevated free T4** and **inappropriately normal TSH**. If free T4 and T3 are high, but **TSH is normal or high (i.e. not suppressed)**, so a **pituitary MRI** should be done to look for a pituitary mass (TSH-secreting adenoma). If there is no pituitary mass, but there is end-organ evidence of hyperthyroidism, a careful family pedigree should be obtained as well as genetic testing for the possibility of thyroid hormone resistance.

The diagnosis of **Secondary hyperthyroidism** should be suspected when **TSH** concentrations are **not suppressed** in the **presence of hyperthyroidism** >>> MRI pituitary.

**Thyrotrophinoma (TSH secreting pituitary tumour):**

It is a rare type of pituitary tumour accounting for approximately less than 1% of cases, the majority (90%) of which are macroadenomas.

Presentation is with features of thyrotoxicosis: sweating, weight loss, lethargy, tachycardia, potential hypopituitarism, erectile dysfunction, diminished libido, and hyponatraemia.

Lab: **Elevated all (TSH, Free T3 and Free T4)**, elevated ALP and hyponatraemia suggests hypoadrenalism.

MRI imaging of the pituitary gland and formal evaluation of visual fields.

### **Graves' disease**

Graves' disease = **Thyrotoxicosis + Goitre + Auto-antibodies** ± Thyroid eye disease (only found in 30%).

Graves' disease is **the most common cause of thyrotoxicosis**.

It is typically seen in women aged 30-50 years.

Features:

- Typical features of thyrotoxicosis
- Specific signs limited to Grave's (see below)

**Specific features** seen in **Graves'** but not in other causes of thyrotoxicosis:

- 1) Eye signs (only in 30% of patients): exophthalmos, ophthalmoplegia.
- 2) Pretibial myxoedema.
- 3) Thyroid bruit,
- 4) Thyroid acropachy.

Autoantibodies:

- **Anti-TSH receptor stimulating autoantibodies** = (Often referred to as **Thyroid Stimulating Immunoglobulins**) (90%).
- **Anti-thyroid peroxidase (TPO) antibodies** (50%).

**NB:** Anti-TSH receptor stimulating autoantibodies is **specific** for Graves' disease and is present in the **vast majority** of cases.

**NB:** A **strong family history** of thyrotoxicosis is **typical** for Graves' disease.

**NB:** **Only** around **30%** of patients with Graves' disease have **eye** disease so the absence of eye signs does not exclude the diagnosis.

**NB:** **Only 50%** of patients with Graves' disease have positive antithyroid peroxidase (TPO) **antibodies**, and therefore their absence does not preclude the diagnosis.

**NB:** The absence of a goitre is also compatible with a diagnosis of Graves' (in addition, a goitre may not be detectable clinically, and may only be seen on imaging).

**NB:** Graves' thyrotoxicosis is associated with **pre-tibial myxoedema**, commonly described as **orange peel skin on both shins**. It is usually associated with: tachycardia, increased levels of SHBG, and **globally increased uptake on thyroid scan**.

**NB:** The most likely associate of Graves' disease is **vitiligo** occurring in approximately 7% of cases. It is important to appreciate that autoimmunity is relatively common in association with thyroid autoimmunity and include type 1 diabetes mellitus, Addison's, pernicious anaemia and Sjögren's.

**NB:** The D.D. for an **eye movement abnormality**, which cannot be explained by a single or multiple cranial nerve palsy is **myasthenia gravis** or **Graves' disease**.

**Myasthenia** is **unlikely** if the patient can look up freely for long periods of time.

**Graves' eye disease can occur with normal thyroid function (FT4 and TSH)**, so the diagnosis can be made by looking for **thyroid stimulating receptor antibody in the serum**.

**Graves' eye disease can occur in euthyroid, hypothyroid or hyperthyroid setting.**

The negative autoantibody argues against this being an autoimmune thyroiditis such as Graves' disease or hashitoxicosis.

**Graves' disease: management**

Despite many trials there is no clear guidance on the optimal management of Graves' disease.

Treatment options include titration of anti-thyroid drugs (ATDs, for example carbimazole), block-and-replace regimes, radioiodine treatment and surgery.

Propranolol is often given initially to block adrenergic effects.

**ATD titration:**

- Carbimazole is started at 40mg and reduced gradually to maintain euthyroidism.
- Typically continued for 12-18 months.
- Patients following an ATD titration regime have been shown to suffer fewer side-effects than those on a block-and-replace regime.

**Block-and-replace:**

- Carbimazole is started at 40mg.
- Thyroxine is added when the patient is euthyroid.
- Treatment typically lasts for 6-9 months.
- Block-and-replace regimes should not be used in pregnancy

The major complication of **carbimazole** therapy is **agranulocytosis** >>>

TTT: **Stop carbimazole** and **start PTU once** the neutrophils count has recovered with follow up CBC.

Carbimazole should be stopped if there is a demonstrable neutropenia/agranulocytosis with neutrophil count below  $1.5 \times 10^9/L$  (1.5-7).

Carbimazole-induced agranulocytosis >>> Carbimazole should be **withdrawn**, infection treated with appropriate **antibiotics** (broad spectrum cephalosporin) and occasionally, granulocyte colony-stimulating factor (**G-CSF**) is required when white count fails to respond.

NB: The incidence of leukopenia/neutropenia with carbimazole is **less than 1%**, so in any particular case **her TLC is normal with normal differential**, there is **no** requirement to stop carbimazole and she should be reassured >>> **Continue carbimazole and reassurance.**

**NB:** the effect of carbimazole has been potentiated by the liver **enzyme-inhibiting** effect of **erythromycin** that was prescribed for upper respiratory tract infection >>> so picture of more hypothyroidism.

### **Radioiodine treatment:**

- RAI is safe and that is why it is given across all ages as a definitive treatment of thyrotoxicosis.
- The **only indication** is toxic multinodular goiter (**TMNG**) or a **single toxic adenoma**.
- Patient should be advised that in the first fortnight there may be an exacerbation of her symptoms and that she will need regular follow up as she may become hypothyroid or her thyrotoxic symptoms may return.
- The most likely side effect of radioactive iodine is **hypothyroidism** with approximately **80%** developing hypothyroidism after therapy. It depends on the dose given, but as a rule the majority of patient will require thyroxine supplementation after 5 years.
- There is no evidence to suggest that RAI is associated with any cancers either thyroid neoplasia or gastric neoplasia.
- **Goitre shrinkage** may occur in only up to **30%** of cases following RAI.
- The risk of **recurrence** after anti-thyroid drugs is **above 50%**.
- **Contraindications:**
  - 1) Pregnancy (pregnancy should be avoided for at least 4-6 months following ttt) and breast feeding.
  - 2) Age < 16 years.
  - 3) Thyroid eye disease is a relative contraindication, as it may worsen the condition.

### **Surgery:**

There is some debate about whether sub-total or total thyroidectomy is the most appropriate option.

With slow re-growth and the possibility of malignant change favouring total thyroidectomy, but this is countered with increased potential risk of post-operative hypoparathyroidism and RLN palsy.

Any patient with **large** goiter with **compression** symptoms and is **euthyroid** (**normal TFTs**), so **anti-thyroid drugs and radioiodine would not be appropriate** and so the best choice option here is **thyroidectomy**.

**Complications:**

- 1) **Transient hypo-parathyroidism** is said to occur in around **8%** of cases, with permanent hypoparathyroidism seen in 1-2% of patients undergoing thyroidectomy >>> **Hypocalcaemia >>> tetany.**
- 2) **Infection** is seen in **1-2%** of patients undergoing thyroidectomy.
- 3) **Bleeding** is less common, seen in around **0.5%** or less.
- 4) **Superior laryngeal nerve palsy** affects **more** patients (**3-4%**).
- 5) **Permanent recurrent laryngeal nerve (RLN) palsy** occurs in **1%**, the inferior thyroid artery runs closest to the recurrent laryngeal nerve.

**Toxic Multinodular Goitre (TMNG)**

- Toxic multinodular goitre describes a thyroid gland that contains a number of autonomously functioning thyroid nodules that secrete excess thyroid hormones.
- Nuclear scintigraphy with technetium 99m reveals patchy uptake.
- The treatment of choice is **radioactive iodine (RAI) therapy**.

**Toxic adenoma (Plummer's disease):****Management (either one of two):**

- 1) **Radioactive iodine (RAI) therapy**: it is **highly effective** for ttt of single toxic adenoma as the **hot** nodule **avidly** takes up radioiodine.
- 2) **Sub-total thyroidectomy.**
- 3) If in **pregnancy**: Medical management by **PTU** (50-300 mg/day) but if failed, Sub-total thyroidectomy to be planned in the 2<sup>nd</sup> trimester.

Long term anti-thyroid drug in single adenoma is inappropriate

Lugol's iodine is used to gain rapid control of thyrotoxicosis prior to surgery.

**EX:** A 42-year-old man with a **thyroid mass**. He tells you that **his mother and brother** both suffered from **thyroid cancer**, his **BP** difficult to manage, his BP is 155/100 mmHg. There is a firm left sided thyroid mass, around 3 cm in diameter, Normal TSH, **High Ca** >>> The next step is **MRI Abdomen >>> exclusion of phaeochromocytoma is crucial before considering thyroidectomy.**

The history of thyroid carcinoma in two first degree relatives raises the possibility of a **familial thyroid cancer syndrome**. The hypercalcaemia further increases suspicion that this is **medullary carcinoma of the thyroid**.



### **Thyroid eye disease**

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

#### **Pathophysiology:**

- It is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation
- The inflammation results in glycosaminoglycan and collagen deposition in the muscles.

#### **Prevention:**

- Smoking is the most important modifiable risk factor for the development of thyroid eye disease.
- Radioiodine treatment may increase the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. **Prednisolone** may help reduce the risk.

Smoking is the most important modifiable risk factor for the development of thyroid eye disease.
--

#### **Features:**

- The patient may be **euo-**, **hypo-** or **hyper**thyroid at the time of presentation.
- Exophthalmos.
- Diplopia
- Conjunctival oedema.
- Optic disc swelling.
- Ophthalmoplegia.
- Inability to close the eye lids, lid lag, and lid retraction may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy.

#### **Management:**

- 1) Topical lubricants and eye patches may be needed to help prevent corneal inflammation caused by exposure.
- 2) **High dose steroids (prednisolone)** are the mainstay of initial therapy for thyroid eye disease.
- 3) Orbital decompression surgery.
- 4) Orbital radiotherapy (controversial).

**NB: Radioiodine exacerbate Graves's ophthalmopathy, and patients with pretibial myxoedema tend to have more severe ophthalmopathy.**

**Monitoring patients with established thyroid eye disease:**

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for **urgent** review by an ophthalmologist (see **EUGOGO** guidelines): (**E**uropean **G**roup **o**n **G**raives' **O**rbitopathy):

- 1) Unexplained sudden deterioration in **vision acuity**.
- 2) Change in intensity or quality of **colour** vision in one or both eyes.
- 3) History of eye suddenly 'popping out' (**globe subluxation**).
- 4) Obvious **corneal opacity**.
- 5) Cornea still visible when the eyelids are closed.
- 6) **Optic disc swelling**.

**NB: Graves' eye disease can occur with normal thyroid function (FT4 and TSH), so the diagnosis can be made by looking for thyroid stimulating receptor antibody in the serum.**

**Subacute (De Quervain's) thyroiditis**

Subacute thyroiditis (also known as De Quervain's thyroiditis) is thought to occur following viral infection (preceded with flu-like symptoms) and typically presents with hyperthyroidism.

Flu-like illness is followed by transient hyperthyroidism, then hypothyroidism, then recovery.

It is probably viral in origin, and results in release of T3 and T4 into the circulation in large quantities. As the condition resolves patients become hypothyroid and then euthyroid.

Thyrotoxicosis is related to **increased release of stored thyroid hormone** rather than increased production of thyroid hormone. As such carbimazole and propylthiouracil are ineffective.

The hypothyroid state may become permanent in 5-10% of patients, but the vast majority go onto to the recovery phase with euthyroid status.

The symptoms of hyperthyroidism will resolve but can take weeks to a few months to do so, and so thyroid status should be monitored.

It is associated with **HLA-B35** and it is thought that a viral antigen binds to HLA-B35 molecules on macrophages.

**Features: (4):**

- 1) Hyperthyroidism.
- 2) Painful tender goitre.
- 3) Raised ESR (around 40- 80 but this is not specific)
- 4) Globally **reduced** uptake on radioactive iodine (**RAI 131 scan**).

The best support for the diagnosis of de Quervain's thyroiditis >>> <b>No</b> RAI 131 scan uptake ( <b>Negligible</b> 4 hour radioiodine thyroid uptake).
---

**Management:**

- Usually **self-limiting** - **most** patients **do not require treatment**
- Thyroid pain may respond to aspirin or other NSAIDs.
- In more severe cases steroids (prednisolone 30-40 mg/day) are used, particularly if hypothyroidism develops. Prednisolone can be stopped when T4 normalises.
- $\beta$ B help control the tremor and anxiety associated with thyrotoxicosis (Propranolol is the most appropriate treatment for her transient symptoms of hyperthyroidism).
- Anti-thyroid drugs have **NO** value in the management of the condition as the excess circulating thyroid hormone is due to the **release of the pre-existing thyroid hormone** as a result of **follicular damage** rather than from increase synthesis.
- If hypothyroidism occurs in the late stages, give thyroid replacement therapy guided by TSH levels.

<p><b><u>(RAI 131 scan):</u></b></p> <ul style="list-style-type: none"><li>- In <b>Graves'</b> disease &gt;&gt;&gt; you would expect <b>homogenous</b> high uptake,</li><li>- Whereas a <b>toxic nodule</b> &gt;&gt;&gt; would show a <b>solitary</b> area of high uptake.</li><li>- In Subacute (De Quervain's) thyroiditis &gt;&gt;&gt; <b>No</b> uptake (minimal up to zero uptake).</li></ul>
---

<p><b>Antibodies</b> such as TSH receptor antibodies and TPO are found only in <b>autoimmune</b> thyroid disease.</p>
---

### **Thyroid storm**

Thyroid storm is a rare but life-threatening sudden complication of thyrotoxicosis exacerbation.

It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature.

It is caused by an exacerbation of hyperthyroidism often due to intercurrent illness, infection as pneumonia, trauma or emergency surgery.

Iatrogenic thyroxine excess does **not** usually result in thyroid storm.

**Clinical features include:** (looks similar to pheochromocytoma)

- **Fever** > 40°C with flushing: is the most characteristic feature.
- **Tachycardia**
- **Hypertension**
- Heart failure
- **Confusion, agitation, psychosis, seizures, coma**
- Nausea and vomiting
- **Abnormal liver function test**

**Investigations:**

- Should look for underlying **precipitants**.
- **TFTs**: classically shows elevated T3 and T4, with **suppressed TSH**.
- **Liver** derangement (raised AST, ALT, LDH, ALP and bilirubin).
- **Renal** impairment,
- Elevated **CPK**
- **Electrolyte** imbalance (due to dehydration): ↓Na, ↓K,
- **Anaemia, thrombocytopenia, leucocytosis,**
- **Hypercalcaemia,** and
- **Hyperglycaemia.**

**Management:**

- Treatment should initially be of any underlying precipitating cause.
- Resuscitation is then often required with oxygen, IV saline and a NGT if vomiting is dominant.
- Symptomatic ttt e.g. paracetamol (NOT aspirin as this can increase T4).
- Anti-thyroid drugs: e.g. carbimazole or propylthiouracil (PTU).

- Lugol's iodine (aqueous iodine) is then given after 4 hours
- **Propranolol** or diltiazem if propranolol is contraindicated
- Dexamethasone - e.g. 4mg IV qds - blocks the conversion of T4 to T3.
- Chlorpromazine can be used if there is severe agitation.
- TTT of heart failure and AF if present
- In severe cases exchange transfusion or haemodialysis may be required.

Untreated, such cases are usually fatal. Even with early diagnosis and treatment, the **mortality is 20-50% (some series 30-75%)**.

Death may be caused by arrhythmia, CHF, hyperthermia or other unidentified factors.

#### **Thyrotoxic hypokalaemic periodic paralysis:**

**EX:** A **26-year-old Chinese** man is admitted on the acute emergency take. He became very unwell after a squash game, complaining of **severe proximal limb weakness**. He has just started treatment for **thyrotoxicosis** (with carbimazole). He is **unable to get up off the bed** due to proximal weakness + **low Serum K >>>>**

#### **Thyrotoxic hypokalaemic periodic paralysis.**

The prevalence of hypokalaemic periodic paralysis is much higher in pts with thyrotoxicosis of **Chinese** origin versus Caucasians, (13-14% vs. 0.1-0.2%).

Attacks can **last from several minutes to hours**, and can be related to **exercise** or a significant carbohydrate load.

Occasionally the respiratory and bulbar muscles may be involved.

The history given is **too acute** to be either Guillain-Barre or myositis, with Guillain-Barre associated with weakness developing over a number of days, and myositis taking a more chronic course with muscle tenderness.

Without the presence of thyrotoxicosis, this picture would fit with hypokalaemic periodic paralysis.

**EX:** A **55-year-old** man with a known history of **Graves'** disease presents to the ER with palpitations, anxiety and fine tremor of both hands.

ECG shows **rapid atrial fibrillation (AF)** with **ventricular rate of 160 to 180/min**. His blood pressure was 110/80 mmHg.

**TSH is low** 0.01 mU/l (N=0.4-5.0) and, **FT4 is high** 60.3 pmol/l (N=10-22).

The immediate management for this patient is >>> **Propranolol**.

**AF** occurs in **10% to 25%** of patients with hyperthyroidism, more commonly in **men** and the **elderly** than in women or patients less than 75-years-old.

Together with the other symptoms described it is generally caused by increased beta-adrenergic tone. **Propranolol is effective in controlling all symptoms** prior to initiation of specific therapy (e.g. carbimazole, which will have a more delayed effect on symptoms).

**Conversion** to sinus rhythm frequently **occurs spontaneously** with treatment of hyperthyroidism.

**Digoxin is very rarely effective alone**, but can be used in combination with propranolol if it is ineffective as a single agent.

Electric or pharmacologic cardioversion would only generally be attempted in patients who are haemodynamically unstable in whom other treatments have been unsuccessful.

AF is likely to **recur** if the underlying cause (i.e. hyperthyroidism in this situation) is not treated.

If AF persists, consideration should be given to anticoagulation in patients who are at risk of embolic events but this would not be the first treatment you would initiate.

### **Subclinical hyperthyroidism**

Subclinical hyperthyroidism is an entity which is gaining increasing recognition. It is defined as:

- Normal serum free thyroxine and triiodothyronine levels.
- With a **TSH** below normal range (usually < 0.1 mu/l).

#### **Causes:**

- Multinodular goitre, particularly in elderly females.
- Excessive thyroxine may give a similar biochemical picture.

The importance in recognising subclinical hyperthyroidism lies in the potential effect on the cardiovascular system (AF or SVT) and bone metabolism (osteoporosis).

It may also impact on quality of life and increase the likelihood of dementia.

#### **Management:**

- TSH levels often revert to normal - therefore levels must be persistently low to warrant intervention.

- A reasonable treatment option is a therapeutic trial of low-dose antithyroid agents for approximately 6 months in an effort to induce a remission.

### Subclinical hypothyroidism

#### Basics:

- **TSH** raised but T3, T4 normal
- No obvious symptoms

#### Significance:

- Risk of progressing to overt hypothyroidism is of 20% per year (higher in men)
- Risk increased by presence of thyroid autoantibodies

#### Treat if: (4):

- 1) TSH > 10
- 2) Thyroid autoantibodies positive
- 3) Other autoimmune disorder
- 4) Previous treatment of Graves' disease

**NB:** Her **lipid** abnormalities are also significant, and driven by the lack of T4; as such, **low dose thyroxine 50 Mcg daily** is a better treatment than starting statin therapy.

### Hypothyroidism:

Hypothyroidism affects around 1-2% of women in the UK and is around 5-10 times more common in females than males.

Symptoms & signs: cold intolerance, weight gain, increasing lethargy, constipation, coarse facial features, periorbital oedema and hair thinning.

#### Primary hypothyroidism:

##### 1) Primary atrophic hypothyroidism:

- Most common cause of hypothyroidism in UK.
- Autoimmune disease, associated with IDDM, Addison's or pernicious anaemia.
- 5 times more common in women

2) Hashimoto's thyroiditis:

- Autoimmune disease as above with goitre (positive microsomal antibodies)
- May cause transient thyrotoxicosis in the acute phase
- 10 times more common in women

3) After thyroidectomy or radioiodine treatment.

4) Drug therapy (e.g. lithium, amiodarone or anti-thyroid drugs such as carbimazole).

5) Dietary iodine deficiency.

**Iodine deficiency** is relatively common in parts of central **Africa**, where the **diet is poor in iodine** and access to **sea fish** is relatively difficult. It may present as **multi nodular goitre without** hypothyroidism, or in severe cases can progress to **frank** hypothyroidism.

Certain drugs are recognised to **interfere with absorption of thyroxine tablets**, these include **Rifampicin, Amiodarone, Calcium** supplements, **ferrous sulphate, cholestyramine, sevelamer** and **PPI (omeprazole)** >>> leading to a hypothyroid status (↑TSH).

**Secondary hypothyroidism (rare):**

From pituitary failure

Other associated conditions

- Down's syndrome
- Turner's syndrome
- Coeliac disease

**N.B:** In European countries and UK >> **primary atrophic hypothyroidism** is the most cause causes of hypothyroidism, whereas in North America >> Hashimoto's thyroiditis appears to account for the majority of cases. The reason for this discrepancy is unclear.

**Hypothyroidism** is known to be associated with **hyper-carotenaemia**. It occurs because of a decrease in conversion from carotene to vitamin A. The consumption of vitamin A in hypothyroidism is also decreased.

Other diseases associated with hypercarotenaemia: DM and Anorexia nervosa.



Any **female** patient with **weight gain**, **menorrhagia** and **dyslipidaemia** ( $\uparrow$ TG) >>> Think of **hypothyroidism** (Hashimoto's). Once thyroxine is commenced, periods improve and hypertriglyceridemia usually begins to resolve.

**NB: Myxoedema coma** may be the **initial** presentation of hypothyroidism, but more usually occurs on background of long standing disease with non-compliance on thyroxine replacement.

It usually occurs in the **elderly** who are typically **non-compliant**.

Myxoedema coma is a rare but very important to diagnose medical emergency.

The clues features are: 'yellowish hue' (referring to carotinaemia), obesity, bradycardia, hypothermia, and coma.

It carries a high mortality and should initially be treated with **IV thyroid hormone** - either T4 or T3 - and **IV hydrocortisone** even before results are obtained.

TTT: **IV thyroxine** and **slow rewarming**, **BUT**

It is **very important to check co-existing hypoadrenalism** by ( $\downarrow$ Na,  $\uparrow$ K,  $\downarrow$ RBS,  $\uparrow$ BUN) as in this case the ttt should be started **firstly with IV hydrocortisone** as giving thyroid hormone alone may worsen an adrenal crisis.

### Hashimoto's thyroiditis (lymphocytic thyroiditis)

Hashimoto's thyroiditis is an autoimmune disorder of the thyroid gland.

It is typically associated with hypothyroidism or subclinical hypothyroidism although there may be a transient thyrotoxicosis in the acute phase.

It is 10 times more common in women.

#### **Features: (3):**

- 1) Features of hypothyroidism (or subclinical hypothyroidism).
- 2) **Goitre**: firm, non-tender.
- 3) **Anti-thyroid peroxidase Ab** (Anti-TPO Ab) (previously known as **thyroid microsomal autoantibodies**) and also anti-Thyroglobulin antibody.

Hashimoto's thyroiditis =

**Hypothyroidism + Goitre + Anti-TPO Ab & Anti-TG Ab**

Hashimoto's thyroiditis is associated with thyroid **lymphoma**.

**Hashimoto's encephalopathy** which is extremely **rare**. You should suspect this as **elevated TSH** is present with **comatose patient** however there may be **no** clinical evidence of thyroid dysfunction.

It can result in altered mental state, myoclonus and ataxia.

It is a **steroid responsive** encephalopathy.

### **Hypothyroidism: management**

#### **Key points:**

- Initial starting dose of levothyroxine should be lower in elderly patients and those with ischaemic heart disease (e.g. 25-50 Mcg/day).
- The BNF recommends that for patients with cardiac disease, severe hypothyroidism or patients over 50 years the initial starting dose should be 25 Mcg OD.
- Following a change in thyroxine dose thyroid function tests should be checked after 6-8 weeks.
- The therapeutic goal is 'normalisation' of the thyroid stimulating hormone (TSH) level.
- As the majority of unaffected people have a TSH value 0.5-2.5 mU/l it is now thought preferable to aim for a TSH in this range.
- There is no evidence to support combination therapy with levothyroxine and liothyronine.

#### **Side-effects of thyroxine therapy:**

- Hyperthyroidism: due to over treatment
- Reduced bone mineral density
- Worsening of angina
- Atrial fibrillation

#### **Interactions:**

Iron: absorption of levothyroxine reduced, give at least 2 hours apart.

**Iron reduces the absorption of thyroxine**

Certain drugs are recognised to **interfere with absorption of thyroxine tablets**, these include **Rifampicin, Amiodarone, Calcium** supplements, **ferrous sulphate, cholestyramine, sevelamer** and **PPI (omeprazole)** >>> leading to a hypothyroid status (↑TSH).

### Pendred's syndrome

Autosomal recessive disorder of defective iodine uptake.

Features:

- 1) Goitre with euthyroidism or mild hypothyroidism
- 2) **Sensorineural** deafness

### Pregnancy: thyroid problems

In pregnancy there is a twofold increase in the levels of thyroxine-binding globulin (↑TBG) this is due to a combination of ↓ hepatic clearance of TBG and ↑ synthesis in response to oestrogen.

The ↑ TBG plateaus at **20 weeks** and then **gradually falls**.

This causes an increase in total thyroxine T4 level but does **not** affect the free thyroxine level.

In pregnancy: **Normal** TSH, **Normal** free T3, **Normal** free T4 , **BUT** high total T3 and **high total** T4 due to increase in the binding Globulin level.

It is a feature of normal pregnancy that **T3** and **T4** show **slight increase** just above the normal range in **first** trimester, with **slight suppression** of **TSH** just below the normal range in up to **15%** of pregnancies during the first trimester & **5%** of pregnancies in the second trimester, this is due to the partial thyroid stimulating action of **β-HCG** and this is a normal variant >>> **observe** and **follow up TFTs**. (It is mimic hyperthyroidism, but NO need for PTU).

**Slightly elevated thyroid hormones FT3 & FT4** with **slightly suppression** of **TSH** may be considered a **normal variant** in the **early** stages of pregnancy especially if there is a history of **hyperemesis** due to **HCG** effect >>> ttt just **observe**.

**TSH falls** in the **first** and **second** trimester, and increases in the third trimester with **subsequent fall** in **free T4** and **T3** in the **third** trimester.

TSH: in **first** and **second** trimester >>> **Low TSH** especially with **hyperemesis**,

But in Third trimester >>>> ↑ TSH >>> **so, low FT3 and low FT4**.

**Thyrotoxicosis:**

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour.

**Graves' disease is the most common cause of thyrotoxicosis in pregnancy.** It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in 2nd and 3rd trimester.

Management:

- **Propylthiouracil (PTU): 50 mg TDS up to 150 mg BID (50-300 mg/day)** has traditionally been the antithyroid drug of choice in pregnancy. This approach was supported by the 2007 Endocrine Society consensus guidelines. It is more highly protein bound than carbimazole and so less is transmitted to foetus cross the placenta. It also has the advantage of being excreted to a lesser extent than carbimazole in breast milk.
- Due to the small risk of fetal abnormalities with carbimazole it is recommended to use **PTU in the first trimester** during organogenesis and **then carbimazole in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester**.
- Women who are taking carbimazole and learn they are pregnant should be switched to PTU at the time of the positive pregnancy test.
- Maternal free thyroxine levels (Free T4) should be kept in the upper limit of the normal reference range to avoid fetal hypothyroidism.
- Thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine risk of neonatal thyroid problems.
- Block-and-replace regimes should not be used in pregnancy as carbimazole crosses the placenta but thyroxine does not, so the block and replace regimen approach could render the neonate profoundly hypothyroid.
- Radioiodine therapy is contraindicated as it would also be taken up by the fetal thyroid.
- Propranolol would ameliorate the symptoms but may impact upon the foetus.
- Lithium is contraindicated in pregnancy as is potassium perchlorate.
- During lactation: the infant's thyroid function should be monitored, although levels in milk are likely too small to affect the infant.
- Patient with hyperemesis gravidarum usually has hyperthyroidism: the emesis is usually driven by high levels of **beta-HCG**. Beta-HCG has a degree of **thyroid stimulating activity**. In the circumstances it is likely that this has **driven TSH down** to below the lower limit of normal. No intervention is necessary, and there is **no** value in using anti-thyroid drugs in this situation.

**Hypothyroidism:**

Key points:

- Thyroxine is safe during pregnancy.
- Serum TSH measured in each trimester (at 6-8 weeks, and then at 16-20 weeks and 28-30 weeks) and 6-8 weeks post-partum.
- Some women require an increased dose of thyroxine during pregnancy.
- Average increase in thyroxine requirements is **25-50 Mcg** and this increased need ceases immediately after delivery.
- If the patient is **stable** with regard to **thyroxine dose pre-pregnancy** then they are likely **to remain stable without any dose adjustment during the pregnancy.**
- Thyroxine treatment should be altered according to the **free T4** levels as TSH may remain elevated even with appropriate treatment (especially in the third trimester).
- Breast feeding is safe whilst on thyroxine.

**Postpartum thyroiditis (PPT)**

It is a variant of chronic autoimmune thyroiditis (**Hashimoto's** thyroiditis).

The exact aetiology is unknown but lymphocytic infiltration of the thyroid is typical, suggesting auto-immunity.

Post-partum thyroid dysfunction is said to occur in up to **10%** of women during the **first year after delivery.**

It is characterised by the presence of **anti-microsomal (Anti-TPO antibodies)** in **30-52% of cases.**

Histologically: **destructive lymphocytic thyroiditis.**

It tends to occur **within the 4 months of delivery** by **transient hyperthyroidism**, followed by a **hypothyroid** phase at 3 to 6 months, followed by **spontaneous recovery** in **one third** of cases within 6-12 months of delivery, **although around 40% eventually go on to develop permanent hypothyroidism.**

It can present with transient hyperthyroidism, but more women present during the **hypothyroid** stage (**↑ TSH**).

The commonest symptom is **fatigue (tiredness/lethargy).**

In **rare** cases thyrotoxicosis may be associated with **psychotic** presentation (she is convinced that her husband is trying to poison her) (D.D. Postnatal depression).

**PPT: Hyper >>> Hypo >>> spontaneous recovery (1/3) or permanent hypo (40%)**

In the remaining two-thirds, a single-phase pattern or the reverse occurs.

Management:

- It is centred on **symptomatic treatment** using **beta-blockers (Propranolol 20 mg TDS)** for relief of tremor or anxiety, and observation for the development of persistent hypo- or hyperthyroidism.
- In patients with **post-partum hypothyroidism**, **low dose thyroxine 50 Mcg** may be used to allow for spontaneous recovery to occur with re-checking of thyroid function off therapy after 6 months of ttt.

**EX:** A 25-year-old woman, she is **10 weeks post-partum** and has been generally unwell for 2 weeks with malaise sweats, tiredness and anxiety.

On examination she is haemodynamically stable, and clinically euthyroid.

TFTs show the following: ↑ FT3, ↑FT4, Low TSH & +ve Anti TPO antibodies.

It is **postpartum thyroiditis**

The appropriate management is **propranolol (NOT carbimazole or PTU)**

### **Sick euthyroid syndrome**

In sick euthyroid syndrome (now referred to as **non-thyroidal illness**) it is often said that **everything (TSH, thyroxine T4 and T3) is low**.

It is a very variable condition and many different pictures can be seen on thyroid testing. For this reason, it is often very difficult to interpret TFTs during intercurrent illness.

**Mild reduction in TSH** during acute illness and increases during recovery.

In the majority of cases however the **TSH level is within the normal range** (inappropriately normal given **the low thyroxine T4 and T3**).

The primary abnormality is **decreased peripheral production of T3 from T4**.

Reverse T3 (rT3) is made instead of normal T3.

The patient will have an **increased reverse T3 (↑rT3)**, which can be measured.

Secondary thyroid failure (pituitary causes) would be a differential, but measurement of **reverse T3** would help **differentiate** between this and sick euthyroid syndrome.

**T4** is often normal or slightly low.

Changes are reversible upon recovery from the systemic illness.

Usually occurred in hospitalized patient at ICU, severe sepsis, heart failure, liver failure, renal failure, end-stage malignancy and starvation.

Thyroid replacement has **no** value and is a subject of **debate**.

Usually no treatment is required, except to treat the underlying disease process.

Sick euthyroid syndrome >>> **TSH: normal or low, T4: low, T3: low**

### Thyroid cancer

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones.

Risk factors for thyroid cancer include: Thyroid adenoma, endemic goiter, Hashimoto's thyroiditis lead to thyroid lymphoma), **FAP**, female, and exposure to radioiodine and radiotherapy.

There is **no screening tests for thyroid cancer**, but there are tests to detect recognised gene mutations.

If thyroid cancer is suspected >>> Thyroid US, scan and FNA.

Since **Thyroglobulin** is synthesized by well-differentiated thyroid carcinomas, it can serve as a useful tumour marker for assessment of **recurrence** of the tumour **but only after total thyroid ablation**.

Type	Percentage	
<b><u>Papillary</u></b>	<b>80%</b>	<p>The most common thyroid carcinoma</p> <p>Often <b>young females &amp;</b></p> <p><b><u>Excellent prognosis</u></b></p> <p>By isotope scanning &gt;&gt;&gt; "<b>cold nodules</b>"</p> <p>Associated with <b><u>FAP</u></b> (Familial Adenomatous Polyposis).</p> <p><b>Trk</b> is a proto-oncogene, its activation is associated with papillary carcinoma.</p> <p>FNA: Large thyrocytes, abnormal nuclei and cytoplasm</p>

		with several mitoses. Psammoma bodies identified. <b>Gardener's syndrome:</b> (see below)
Follicular	10%	Spread through blood vessels
Medullary	5%	Cancer of <u>parafollicular cells</u> , secrete <u>calcitonin</u> ( $\uparrow$ serum Ca), part of <u>MEN-2</u>
Anaplastic الأناتية اوحش حاجة	1%	<b>Very poor prognosis</b> ☹  The vast majority (~90%) having <b>local invasion</b> (cervical lymph glands) and <b>local infiltration</b> (particularly the trachea) at diagnosis.  So can cause <b>pressure</b> symptoms ☹  Upper airways obstruction frequently requires <b>tracheostomy</b> .  <b>Lung &amp; bone metastases</b> are common at presentation (~ 50%).  <b>Not</b> responsive to treatment  <b>Death</b> from massive local extension usually occurs within <b>3-36 months</b> .
Lymphoma	Rare	Associated with <b>Hashimoto's</b> and other <b>autoimmune</b> disorders  TTT: Respond dramatically to irradiation.

**Gardener's syndrome:**

It is a **rare** familial **autosomal dominant** condition characterized by **multiple small** and **large** intestinal **polyposis** tumours + **Osteomas** + **soft tissue tumours** (multiple lipomas, fibromas, and epidermoid cysts).

It carries an increased risk of **papillary carcinoma of the thyroid**.

**Colonic carcinoma** develops in 7% of individuals by age 21 years, 50% by age 39 years and 90% by age 45 years.

**Colectomy** is recommended once polyps appear.



**Management of papillary and follicular cancer:**

- 1) Total thyroidectomy.
- 2) Followed by radioiodine (I-131) to kill residual cells.
- 3) Follow up yearly with thyroglobulin levels to detect early recurrent disease (only after total thyroid ablation).

Factors that suggest a **poor prognosis** in thyroid cancer include: **male sex**, increasing **age**, poorly differentiated histological features, and distant spread.

**Skin disorders associated with thyroid disease****Skin manifestations of hyperthyroidism:**

- Pretibial myxoedema: erythematous, oedematous lesions above the lateral malleoli, No treatment is usually required.
- Thyroid acropachy: clubbing
- Scalp hair thinning
- Increased sweating

**Skin manifestations of hypothyroidism:**

- Dry (anhydrosis), cold, yellowish skin.
- Non-pitting oedema (e.g. hands, face)
- Dry, coarse scalp hair, loss of lateral aspect of eyebrows
- Eczema
- Xanthomata

**N.B:** Pruritus can occur in both hyper- and hypothyroidism.

## Thyroid function tests (TFTs)

The interpretation of thyroid function tests is usually straightforward:

Diagnosis	TSH	Free T4	Notes
Thyrotoxicosis (e.g. Graves' disease)	Low	High	In T3 thyrotoxicosis the free T4 will be normal
Primary hypothyroidism (primary atrophic hypothyroidism)	High	Low	
Secondary hypothyroidism	Low	Low	Replacement <u>steroid</u> therapy is required <u>prior</u> to thyroxine.
Sick euthyroid syndrome (non-thyroidal illness)	Low	Low	Common in hospital inpatients T3 is particularly low in these patients, TSH may be normal in some cases  <b>rT3</b> is used to differentiate
Poor compliance with thyroxine	High	Normal	The TSH level is high. This implies that over recent days/weeks her body is thyroxine deficient.  However, the free T4 is within normal range.  The most likely explanation is that the <u>Pt. started taking the thyroxine properly just before the blood test.</u> This would correct the thyroxine level T4, T4 is converted to T3. But the TSH takes longer to normalise.  ( <b>N</b> freeT4, <b>N</b> free T3, but <b>↑TSH</b> )
Sub-clinical hypothyroidism	High	Normal	

Diagnosis	TSH	Free T4	Notes
Steroid therapy	Low	Normal	
Sub-clinical hyperthyroidism	Low	Normal	

Situation	TSH	ft4	ft3
Over-replacement with thyroxine	Low	High	Normal/High
Sick euthyroid syndrome	Normal/ High	Low	Normal/Low
Subclinical hypothyroidism	<b>High</b>	Normal	Normal
Subclinical hyperthyroidism	<b>Low</b>	Normal	Normal
TSH-secreting tumour	<b>High</b>	<b>High</b>	<b>High</b>
Untreated hypopituitarism	Low/Low normal	Low/Low normal	Low/Low normal

**Over replacement of thyroxine:** (↑ Free T4, still low TSH, Normal or high FT3)

This is a **very common** pattern of thyroid function tests. The main differential diagnosis is **subclinical hypo-thyroidism** and drug treatment with steroids, amiodarone or lithium.

**Overdoses of thyroxine** (as suicidal tendency) are relatively rare, and a number of strategies have been described in their management.

In reality, patients may be partially protected from thyroid hormone excess by production of reverse T3.

As such, the vast majority can be managed with regular **propranolol** to alleviate symptoms of tachycardia and anxiety.

In severe cases, **Plasmapheresis** to remove protein bound thyroxine, and **cholestyramine** to reduce enterohepatic circulation of thyroxine have been advocated.

The most likely investigation to differentiate between **self-administration of thyroid hormone** and **endogenous causes of thyrotoxicosis** is >>>> **Radioactive uptake thyroid scan.**

- Graves' disease is associated with diffusely increased radioactive uptake in the thyroid.
- A solitary hot nodule demonstrates increased uptake in one area, with decreased uptake elsewhere,
- Toxic multinodular goitre, multiple areas of increased uptake.
- In **thyrotoxicosis factitia**, uptake is **globally reduced**.
- Free T3, free T4 and thyroid binding globulin are **unhelpful** in determining whether thyrotoxicosis is due to exogenous administration of thyroid hormone or not.

**Thyroglobulin** is the precursor of thyroid hormones, therefore if undetectable, indicates an external source of thyroid hormone has been administered (Factitious thyrotoxicosis).

Also used for follow up of recurrence of thyroid tumour, only after excision.

So in **Factitious thyrotoxicosis**: **1)** globally reduced radioactive uptake thyroid scan and **2)** Thyroglobulin is undetectable.

### **McCune-Albright syndrome:**

It is due to a **mutation in a G-protein**.

This results in spectrum of **triad** of:

- 1) Polyostotic fibrous dysplasia,**
- 2) Café-au-lait spots and**
- 3) Endocrinopathies (precocious puberty).**

It is established on clinical grounds, with the presence of increased risk of **bony fibromas** with **osteosarcoma** leading to possible multiple **pathological fractures** and **breast carcinoma** and **thyrotoxicosis**.

Thyroxine is mostly bound to thyroxine binding globulin in the circulation. **Oestrogen therapy as in OCP** is associated with **elevation of thyroxine binding globulin** in the serum >>> Thus the total serum thyroxine may be misleading in this case, and **serum free thyroxine** will confirm whether this patient is hypothyroid or euthyroid.

So any patient on OCP >>> should test **free** not total T4.

Heparin is having an "in vitro" effect on thyroxine (T4) levels.

**IV heparin** interferes with the thyroid function tests assay on occasions displacing bound thyroid hormone >>> ↑ **Free T4** with normal TSH.

### Calcium metabolism

The **two** hormones which primarily control calcium metabolism are:

- Parathyroid hormone (**PTH**).
- 1, 25-dihydroxycholecalciferol (calcitriol, the active form of **vitamin D**).

Other hormones include:

- Calcitonin: secreted from the parafollicular cells (C-cells) of the thyroid gland
- Thyroxine
- Growth hormone

#### **Actions of parathyroid hormone (PTH):**

- 1) Increases plasma calcium, **decreases plasma phosphate**
- 2) Increases renal tubular reabsorption of calcium
- 3) Increases osteoclastic activity
- 4) Increases renal conversion of 25-hydroxycholecalciferol to 1, 25-dihydroxycholecalciferol.
- 5) Decreases renal phosphate reabsorption**

#### **Actions of 1, 25-dihydroxycholecalciferol (Vit D):**

- 1) Increases plasma calcium and plasma phosphate
- 2) Increases renal tubular reabsorption of calcium and phosphate.
- 3) Increases gut absorption of calcium.**
- 4) Increases osteoclastic activity.

- 5) **Suppresses synthesis of type 1 collagen**, this is balanced by upregulation of osteocalcin, the balance of these changes is an increase in bone mineralisation.
- 6) **IL 6 antagonist**

**Vitamin D >>> increases both plasma calcium and plasma phosphate levels.**

**NB:** The **intestinal absorption of calcium** is facilitated by **1, 25 dihydroxy-vitamin D**, which stimulates the microvillous membrane of the enterocyte to synthesise the calcium-binding carrier protein necessary for active calcium ion absorption.

**I.e. there is no direct effect of PTH on GIT regarding ca absorption.**

### Hypercalcaemia: causes

The most common causes of hypercalcaemia are:

- 1) **Malignancy** (bone metastases, myeloma, PTHrP from squamous cell lung cancer) and
- 2) **Primary hyperparathyroidism** (**NOT** secondary or tertiary type).

Other causes include

- 1) Granulomas: Sarcoidosis, also Tuberculosis and histoplasmosis.
- 2) Vitamin D intoxication
- 3) Acromegaly
- 4) Thyrotoxicosis
- 5) Milk-alkali syndrome: Rennie antacid tablets and calcium tablets
- 6) Drugs: thiazides, calcium containing antacids
- 7) Dehydration
- 8) Addison's disease
- 9) Paget's disease of the bone: usually Ca is normal, but hypercalcaemia may occur with prolonged immobilisation.

In **solid tumours** like breast cancer, **hypercalcaemia** is caused by **tumour production** of **PTHrP** (parathyroid hormone-related protein). This acts on **osteoclasts** in bones to increase bone resorption and promote ca release from bone. It also inhibits ca excretion in the distal tubule of the kidney.

Hypercalcaemia of malignancy is **NOT** thought to be a product widespread bony metastasis and bone destruction, or tumour production of PTH or Vit D.

PTH-related peptide can be raised in a number of malignancies. Old PTH assays may have also picked up PTH-rp but **modern** assays are able to **distinguish** between the two.

The plasma **PTH** is the best single test for differentiating between hypercalcaemia due to **parathyroid** over activity and that due to **non-parathyroid** cause.

**Primary hyperparathyroidism** can be associated with a plasma PTH within the normal range.

The normal response to hypercalcaemia due to **non-parathyroid cause** is **suppression** of the plasma PTH below the lower reference limit.

PTH levels within the reference limit or inappropriately high is suggestive of parathyroid disease.

PTH stimulates bone resorption and formation, whereas PTH-rp stimulates only bone resorption, with very low osteoblastic activity, and thus **ALP levels are usually within the normal range**.

So in malignancy: ↑ **Ca** with **low PTH** and **normal ALP**.

**EX:** Male patient 50 years old, well and fit, just takes OTC multivitamins, has **high serum ca** and **PTH is within normal >>> Primary hyperparathyroidism (NOT Vit D excess)**.

So any Pt with high serum calcium >>> 1<sup>st</sup> check **PTH**, if high or normal so it is primary hyperparathyroidism, but if suppressed PTH so it is hypercalcaemia due to non-parathyroid cause.

If primary hyperparathyroidism >>> **Then** you should do **24 hours urinary calcium** or urinary calcium/creatinine ratio to distinguish primary hyperparathyroidism from FHH (see below).

FHH is often misdiagnosed as primary hyperparathyroidism but may be distinguished from the latter by the **positive family history** together with the **markedly low urine calcium excretion**.

**24 hours urinary calcium** or **urinary calcium/creatinine ratio** may be useful if used in comparison to the serum calcium in order to **distinguish** familial

hypocalciuric hypercalcaemia (**FHH**) from primary hyperparathyroidism (it is lower than in 1ry hyperparathyroidism and the urinary calcium/creatinine ratio is usually less than 0.01).

It should be done as **first test** in **any patient with hypercalcaemia**.

FHH is a **benign** cause of hypercalcaemia and is a hereditary disease with **autosomal dominant** transmission with high penetrance, and is characterized by moderate chronic hypercalcaemia and normal or moderately elevated PTH.

The importance of this FHH condition is that the hypercalcaemia rarely leads to significant clinical signs and parathyroidectomy is unsuccessful as a therapy.

FHH is unlike hyperparathyroidism it is not associated with any specific abnormality, is benign and requires **no treatment**.

One of the key differentiating features between myeloma and monoclonal gammopathy of uncertain significance (MGUS) is the **absence** of complications such as immune paresis, hypercalcaemia and bone pain. (**So in MGUS >>> No hypercalcaemia**)

The **calcium-sensing receptor (CaSR)** is a G protein-coupled receptor, which allows the **parathyroid chief cell**, the **thyroidal C cells**, and the **ascending limb of loop of Henle** to respond to changes in the extracellular Ca concentration.

**Three** uncommon human disorders are due to abnormalities of the CaSR gene:

- (1) FHH (Familial benign Hypocalciuric Hypercalcaemia).
- (2) Neonatal severe hyperparathyroidism.
- (3) Autosomal dominant hypocalcaemia with hypercalciuria.

**Primary** hyperparathyroidism is associated with hypercalcaemia and an inappropriately raised parathyroid hormone, the phosphate level is typically low.

**Secondary** hyperparathyroidism is associated with hypocalcaemia and an appropriately elevated parathyroid hormone level, the phosphate level is variable depending upon the aetiology (high in renal failure, low in vitamin D deficiency).

**Tertiary** hyperparathyroidism. Biochemically this is characterised by raised calcium, raised (or sometimes normal) phosphate and grossly elevated parathyroid hormone levels.

**Hypercalcaemia of malignancy and iatrogenic hypercalcaemia** would both be associated with a high calcium and low parathyroid hormone level.



**NB: Calculation of corrected calcium:**

Add 0.1 mmol/L of calcium for every 4 g/dL that the albumin level is below 40 g/dL.

**EX:** Calcium = 2.6 mmol/L and serum albumin = 24 gm/L

<b>Corrected calcium</b>	= 2.6 + (((40-24)/4) × 0.1)
	= 2.6 + ((16/4) × 0.1)
	= 2.6 + (4 × 0.1)
	= 2.6 + 0.4
	<b>= 3.0 mmol/L</b>

**Hypercalcaemia: management**

- 1) The initial management of hypercalcaemia is rehydration with **normal saline**, typically **3-4 litres/day**.
- 2) Following rehydration **bisphosphonates** may be used like IV Zoledronic acid (Zometa 4 mg IVI). They typically take 2-3 days to work with maximal effect being seen at 7 days.
- 3) Other options include: **calcitonin** - quicker effect than bisphosphonates, its use is limited by its association with anaphylaxis, so only used in resistant cases.
- 4) **Steroids** in sarcoidosis.
- 5) **Furosemide** should only be given **with** fluid resuscitation. It is calciuric. It may be useful in patients who cannot tolerate aggressive fluid rehydration as in ventricular strain and pulmonary oedema.
- 6) **General measures**
  - a. Minimize immobilization.
  - b. Stop thiazide, NSAIDS and drugs that contains Ca & Vit D.

**Hypercalcaemia of malignancy:**

This is an **oncological emergency** affecting **20-40%** of patients with advanced cancer.

It is the most common life-threatening metabolic complication of malignancy.

Serum Ca<sup>++</sup> **above 3 mmol/l** is associated with cardiac arrhythmia, coma, pancreatitis and urgent ttt is required.

**Hyporeflexia** is a common clinical sign in patients with significant hypercalcaemia (especially **more than 3 mmol/L**) (N= 2.2-2.6).

Other signs include the classic mnemonic '**bones, stones, abdominal groans and psychic moans**'.

**Abdominal pain** is commonly seen and there is increased risk of **acute pancreatitis**.

Also there is **nausea, vomiting, dehydration** and **polyuria, polydipsia** (**Nephrogenic DI**)

NB: Hypercalcaemia may induce **nephrogenic DI**.

**ECG: bradycardia, short QT interval**, prolonged PR interval (is possible, but is much less common than QT shortening.), widened T waves and arrhythmias **Ventricular fibrillation** has been reported in extreme cases.

**Bisphosphonates** inhibit bone resorption by **osteoclasts**, and are the **first** line pharmacological treatment of hypercalcaemia of malignancy. However, they **take 3-4 days** to reduce the calcium level, and **can result in worsening renal** function. It is therefore critical to **fully hydrate the patient prior to giving them** so in clinical practice we tend to give **3 litres of fluids over a 12-16 hrs period prior** to giving bisphosphonate. Clearly, this needs to be altered if the patient is at risk of fluid overload and cardiac failure.

Since Hypoalbuminaemia is common in malignancy and will affect the total serum Ca concentration, so use this **formula**:

**The corrected serum Ca =**

**Measured Ca (mmol/L) + (40-serum albumin gm/dl) X 0.027.**

**Hypercalcaemia** associated with **raised ALP** is more likely to be due to **bony metastases**;

**Hypercalcaemia** with **normal ALP** raises the possibility of **underlying** organ tumour like **myeloma**.

### Primary hyperparathyroidism

In exams primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level. It is most commonly due to a solitary adenoma.

The prevalence of hyperparathyroidism is said to be **four per 1000 in women over 60**, and is 2 to 3 times more common in women than men.

The **PTH** level in **primary** hyperparathyroidism may be **normal** or less than twice the upper limit of normal.

A **high** or **even normal PTH** concentration **in the presence of hypercalcaemia** would support the diagnosis of primary hyperparathyroidism.

**Hypercalcaemia + elevated PTH + low phosphate >>> indicating primary hyperparathyroidism.**

The hypophosphatemia is due to the **reduced renal reabsorption of phosphate**.

When patient has grossly elevated calcium and in the context of the **extremely high PTH** concentration >>> **Parathyroid carcinoma** should be considered.

**Causes of primary hyperparathyroidism:**

- 1) 80%: solitary adenoma
- 2) 15%: hyperplasia
- 3) 4%: multiple adenoma
- 4) 1%: carcinoma

**Features - 'bones, stones, abdominal groans and psychic moans':**

- Polydipsia, polyuria
- Peptic ulceration/constipation/pancreatitis
- Bone pain/fracture, especially if the PTH is elevated
- Renal stones and renal medullary calcification.
- Depression, confusion
- Hypertension

**Associations:**

- Hypertension.
- Multiple endocrine neoplasia: MEN I and IIa.

**Investigations:**

- 1) Raised calcium, low phosphate
- 2) PTH may be raised or normal
- 3) Technetium-MIBI subtraction scan

**Treatment:**

- **Total parathyroidectomy.**
- Bisphosphonates.

**Indications for parathyroidectomy including:**

- 1) **Serum** albumin-adjusted **calcium** greater than 0.25 mmol/L above the normal range (**Ionized Ca++ > 3 mmol/l**).
- 2) **24 hour total urinary calcium excretion** greater than 10 mmol (400mg)
- 3) **Creatinine clearance** reduced by 30% or more
- 4) **DEXA** Bone mineral density **T-score less than -2.5 at any site**
- 5) **Age less than 50**
- 6) Unwillingness of patient to follow advice of medical surveillance.

**If unfit for surgery >>> medical parathyroidectomy by Cinacalcet** (which is used in **primary, secondary and tertiary** hyperparathyroidism).

Prior to any surgical intervention for hyperparathyroidism, it is crucial to **rule out pheochromocytoma** as a co-existing diagnosis as in MEN 1 or 2a.

**Secondary hyperparathyroidism as in CKD** is with raised creatinine, borderline low calcium, and raised phosphate.

In secondary hyperparathyroidism, hypocalcaemia stimulates the parathyroid to produce excess PTH. **It may progress to tertiary hyperparathyroidism**, whereby the parathyroid becomes **autonomous** in producing PTH even without the stimulus of hypocalcaemia, but primary does not.

Phosphate retention and a lack of hydroxylated vitamin D drives increased levels of PTH as the body strives to retain calcium.

Patients with renal disease however are not treated for hyperparathyroidism **until the PTH level breaches twice the upper limit of the normal range**. This is because of the **risk of precipitating adynamic bone disease**.

A slightly elevated PTH level is actually desirable in the management of renal bone disease. **Suppression** is not generally necessary **until levels exceed 300 ng/L**.

Usual **first** line therapy is **weekly 1-Alpha**, because the drive for increased PTH comes at least in part from low levels of 1, 25-OH Vitamin D, and it is used when serum calcium is low-normal and PTH is above twice the upper limit of normal range.

If Vit D replacement fails to achieve a reduction of PTH levels, then **surgery** may be considered.

**Cinacalcit** is a PTH antagonist, it is a **calcimimetic** which is used to treat secondary hyperparathyroidism; It mimics the effect of calcium on the parathyroid glands (and elsewhere) with the intention of **limiting parathyroid hormone (PTH) production** and deleterious effects on bone architecture.

It is **only** recommended by NICE for the management of patients with hyperparathyroidism who are on dialysis and **not fit for surgery**.

In **tertiary hyperparathyroidism**: ESRD with regular dialysis, when PTH production becomes autonomous, has marked **high PTH** (> twice upper normal), **high Calcium**, **high phosphate** >>> TTT: PTH antagonist **Cinacalcet**, in conjugation with other measures like a **low phosphate diet**, **phosphate binder such as Sevelamir**, but **only if** the patient is unable to undergo **surgery**.

I.e. The most appropriate treatment once **tertiary hyperparathyroidism** has developed is **parathyroidectomy**.

**EX**: ESRD Pt with ↑PTH and ↑Ca >>> TTT: **Parathyroidectomy or Cinacalcet (only if not well fit for surgery)**.

### **Familial isolated hyperparathyroidism (FIHP):**

FIHP is a **rare** condition characterised by an **autosomal dominant** mode of inheritance. It is closely related to **MEN1** but the development of other tumours is not seen over the course of many years, despite the fact that a number of MEN1 germline mutations are now described.

**Parathyroidectomy** is the treatment of choice.

**EX**: A 45-year-old man is referred to the endocrine clinic. He has been found on **routine** screening to have an **isolated elevated calcium** of 2.9 mmol/L. There is no past medical history of note, and clinical examination is entirely normal. His father and uncle have been reported to have high calcium levels but had no other significant problems >>> **FIHP**.

### **Hyperparathyroidism jaw tumour syndrome:**

It is a syndrome of hyperparathyroidism and fibro-osseous tumours of the jaw. It is described as having increased incidence in Romany families.

**Sevelamer** is a **non-aluminium containing phosphate binder**, and as such is a reasonable option for patients with ESRD with raised serum phosphate levels.

Aluminium hydroxide was previously the drug of choice, but due to concern about accumulation of aluminium, leading to possible aluminium related dementia, it has now fallen out of favour.

Alternatives to sevelamer include calcium acetate and calcium carbonate, although there are theoretical concerns about use of calcium containing salts and increased risk of tissue calcification.

### **Hypocalcaemia: causes and management**

The clinical history combined with **PTH** levels will reveal the cause of hypocalcaemia in the majority of cases.

Causes:

- **Vitamin D deficiency** (osteomalacia = ↓ s Ca + ↓ s phosphate + ↑ ALP)  
>>Proximal myopathy is often a presenting feature of osteomalacia.
- **Chronic renal failure**
- **Hypoparathyroidism** (e.g. post thyroid/parathyroid surgery)
- Pseudohypoparathyroidism (target cells insensitive to PTH)
- **Rhabdomyolysis** (initial stages)
- **Magnesium deficiency** (due to end organ PTH resistance), EX: Cisplatin.
- Massive blood transfusion.
- Acute pancreatitis may also cause hypocalcaemia.
- Contamination of blood samples with EDTA may also give falsely low calcium levels.

Management:

- Acute management of severe hypocalcaemia is with IV replacement. The preferred method is with **IV calcium gluconate, 10ml of 10% solution over 10 minutes.**
- IV calcium chloride is more likely to cause local irritation.
- ECG monitoring is recommended.
- Further management depends on the underlying cause.

### **Hypomagnesaemia**

Most of the body's magnesium is **intracellular** with **only 1% being extracellular**, in blood and interstitial fluid.

This means that blood magnesium levels do not necessarily correspond with whole body magnesium status.

Cause of low magnesium:

- **Drugs:** diuretics, cisplatin, cyclosporine and cardiac glycosides
- **Malabsorption syndromes**
- **Diarrhoea**
- **Hypokalaemia, hypocalcaemia**
- **Total parenteral nutrition**
- **Alcohol**
- **Metabolic acidosis**
- **Renal diseases:** pyelonephritis, GN, ATN and interstitial nephritis.

Features:

- Paraesthesia
- Tetany
- Seizures
- Arrhythmias
- Lethargy, fatigue, muscle weakness, fasciculations
- changes in personality
- Lack of appetite.
- Decreased PTH secretion → **hypocalcaemia**
- ECG features similar to those of hypokalaemia
- Exacerbates digoxin toxicity

### **Vitamin D resistant rickets**

Vitamin D-resistant rickets is an **X-linked dominant** condition which usually presents in **infancy** with **failure to thrive**.

Therefore an **affected female** will transmit the disease to **50% of her sons** and **50% of her daughters**.

An **affected male** will transmit the condition to **all of his daughters** but **none of his sons**.

It is caused by **impaired phosphate reabsorption** in the renal tubules.

Features:

- **Failure to thrive**
- **NORMAL serum calcium, low phosphate, elevated ALP.**
- X-ray changes: **cupped metaphysis** with **widening of the epiphyses**.

Diagnosis is made by demonstrating **increased urinary phosphate**.

Management:

- High-dose vitamin D supplements.
- Oral phosphate supplements.

NB: **Oncogenic osteomalacia**:

Certain **tumours** including **mesenchymal** tumours, **adenocarcinoma** (e.g. prostatic carcinoma) and **haematological** malignancies such as **myeloma** and **CLL** appears to produce **phosphaturic substances**.

Patient presents with **bony pain** and /or **fracture**, **profound proximal myopathy** and **severe hypophosphataemia** usually accompanied by **marked reduction of concentration of 1, 25-OH Vitamin D**.

**TTT: Vit D metabolites and phosphate supplements.**

## Hypoparathyroidism

Three types of hypothyroidism:

- 1) Primary Hypoparathyroidism.
- 2) Pseudo-hypoparathyroidism.
- 3) Pseudo-pseudo-hypoparathyroidism.

**Primary Hypoparathyroidism:**

- ↓ **PTH** secretion.
- E.g. secondary to thyroid surgery (N.B: this may seem an oxymoron, but most medical textbooks classify hypoparathyroidism which is secondary to surgery as being 'primary hypoparathyroidism').



- Low calcium, high phosphate.
- Treated with alfacalcidol.

The main symptoms of Hypoparathyroidism are secondary to hypocalcaemia:

- As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen a result of **neuromuscular excitability**.
- Tetany: muscle twitching, cramping and **carpopedal spasm**
- **Paraesthesia** (usually **perioral** around mouth, fingers and toes)
- ECG: **prolonged QT interval**
- **With worsening hypocalcaemia:** Bronchospasm, Laryngospasm and Seizures.
- If **chronic >> depression, cataracts**
- **Trousseau's sign:** carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic. It is seen in around 95% of patients with hypocalcaemia and around 1% of normocalcaemic people
- **Chvostek's sign:** tapping over parotid causes facial muscles to twitch. It is seen in around 70% of patients with hypocalcaemia and around 10% of normocalcaemic people.

Hypocalcaemia >> <b>Trousseau's</b> sign is <b>more sensitive</b> and <b>specific</b> than Chvostek's sign
--

### **Pseudo-hypoparathyroidism:**

- Target cells being insensitive to PTH (**insensitivity to PTH**).
- Two types:
  - Type I: there is a complete receptor defect.
  - Type II: the cell receptor is intact.
- **Due to abnormality in a Gs protein receptor (alpha unit).**
- **Autosomal dominant** fashion (It was previously thought to be an X-linked dominant condition).
- There is resistance to a variety of hormones that act via **cAMP** (including PTH, TSH and gonadotrophins).

- **Low calcium, high phosphate, high PTH (= same lab like 2ry hyperparathyroidism).**
- **Also** there is raised TSH with low T4 and raised gonadotrophins.
- Associated with (features): low IQ, cognitive impairment, short stature, obesity, shortened 4th and 5th metacarpals, brachymetacarpals, brachymetatarsals, SC calcification nodules, soft tissue calcification/ossification, round face, stocky habitus, and dental hypoplasia.
- Hypocalcaemia causes paraesthesia, cramps, tetany, and carpopedal spasm, whereas hypothyroidism causes fatigue.
- Diagnosis is made by measuring urinary cAMP and phosphate levels following an infusion of PTH:
  - In hypoparathyroidism this will cause an increase in both cAMP and phosphate levels.
  - In pseudohypoparathyroidism type I neither cAMP nor are phosphate levels increased.
  - Whilst in pseudohypoparathyroidism type II only cAMP rises but phosphate levels do not change.
- The mainstay of treatment is **calcium** and **vitamin D**.

The diagnosis is pseudo-hypoparathyroidism confirmed with **genetic analysis** and with a **failure of cAMP rise following PTH**.

### **Pseudo-pseudo-hypoparathyroidism:**

- Similar phenotype to pseudohypoparathyroidism but normal biochemistry.

## Multiple Endocrine Neoplasia (MEN)

MEN type I	MEN type IIa	MEN type IIb
Wermer Syndrome	Sipple Syndrome	
<p><u>3 P's:</u></p> <ul style="list-style-type: none"> <li>➤ <b>Parathyroid</b> (95%): hyperparathyroidism due to parathyroid hyperplasia.</li> <li>➤ <b>Pituitary</b> (70%): prolactinomas.</li> <li>➤ <b>Pancreas</b> (50%): e.g. Insulinoma, Carcinoid, Gastrinoma (leading to recurrent peptic ulceration).</li> <li>➤ Also: adrenal and thyroid.</li> </ul>	<ul style="list-style-type: none"> <li>➤ <b>Medullary</b> thyroid cancer (MTC) (70%).</li> </ul> <p><u>2 P's:</u></p> <ul style="list-style-type: none"> <li>➤ <b>Parathyroid</b> (60%).</li> <li>➤ <b>Phaeochromocytoma</b> (95%).</li> </ul>	<ul style="list-style-type: none"> <li>➤ <b>Medullary</b> thyroid cancer (MTC).</li> </ul> <p><u>1 P:</u></p> <ul style="list-style-type: none"> <li>➤ <b>Phaeochromocytoma</b>.</li> <li>➤ Marfanoid body habitus.</li> <li>➤ Mucosal Neuromas.</li> <li>➤ Medullated corneal nerve fibers.</li> <li>➤ Intestinal polyps: (identified histologically as intestinal ganglioneuromas and are usually asymptomatic).</li> </ul>
<p>MEN1 gene. (On chromosome <b>11q13</b>)</p> <p>Most common presentation = <b>hypercalcaemia</b>.</p>	<p><u>RET</u> oncogene. (On chromosome 10)</p>	<p><u>RET</u> oncogene. (On chromosome 10)</p>

**N.B:** MEN is inherited as an **autosomal dominant** disorder.

**N.B:** The high incidence of parathyroid tumours and hypercalcaemia make **serum calcium** a useful indicator of MEN type 1 in suspected individuals (**90%** of patients with MEN type 1 have hypercalcaemia).

**N.B:** In **Phaeochromocytoma** and suspected MEN IIa >>> Check for **medullary carcinoma of the thyroid (C cell hyperplasia) firstly** then PTH by measuring **serum calcitonin** using **pentagastrin stimulation test**. If patients with MEN-2 are not identified by screening, often at the time of presentation **medullary thyroid carcinoma with metastases to cervical lymph nodes has already occurred**.

**NB:** In **MEN-2a** the initial diagnostic investigation of choice for pheochromocytoma is by **24 hr urinary catecholamine assay**, where the diagnosis is proven, it is sensible to screen for medullary thyroid carcinoma via **pentagastrin testing**.

**NB:** The **pentagastrin stimulation test** measures calcitonin levels at 2 and 5 minutes however, a rise in calcitonin is suggestive of medullary thyroid carcinoma. Elevated basal levels of calcitonin are not specific as are seen in pregnancy, carcinoid, pernicious anaemia, CRF and thyroiditis.

**NB: Renal disease** in **MEN-2** is characterised by **stone**, rather than tumour formation.

**RET** oncogene encodes a receptor tyrosine kinase & is associated with **MEN type II a & b**.

<p><b>EX:</b> Female Pt. with galactorrhoea + amenorrhea + Hypogonadotrophic hypogonadism (low FSH, LH, Estradiol) + High prolactin + Recurrent gastritis &gt;&gt;&gt; MEN I</p>
--

<p><b>EX:</b> Male 35 years old has ↑ <b>BP</b> 170/110 mmHg &amp; ↑ <b>Ca</b> 3.1 mmol/L &gt;&gt; <b>MEN2A</b> , HTN is due to pheochromocytoma &amp; high Ca is due to hyperparathyroidism.</p>
---

<p>MEN II A &amp; B there is medullary thyroid cancer (MTC) and pheochromocytoma.</p>
---

<p>In MEN II B &gt;&gt;&gt; In addition, there is characteristic facial appearance with swollen lips; tumours of the mucous membranes of the eyes, mouth, tongue and nasal cavity; enlarged colon; and skeletal abnormalities.</p>
--

<p>In <b>MEN-2b</b>, Intestinal <b>ganglioneuromatosis</b> affects around <b>75%</b> of cases. Neuromas involve the autonomic nerves of both the myenteric and submucosal plexi and can cause <b>poor suckling</b> with <b>failure to thrive</b>, <b>constipation</b>, <b>diarrhoea</b>, <b>recurrent pseudo-obstruction</b> and <b>toxic megacolon</b>.</p>
--

<p>In addition, <b>medullary thyroid carcinoma</b> is a feature of MEN-2b. This <b>metastases in early life</b>, and is therefore often <b>incurable by age 4 years</b> and leads to <b>early</b></p>
---

**death. Total thyroidectomy** is the **only** established treatment for medullary thyroid carcinoma, the timing of which must take into account risks and benefits for small children.

**EX:** A 29-year-old woman brings her **6-week-old child**. She is concerned as the child has **poor suckling** and has been admitted to the ER on two occasions with **possible bowel obstruction** but later discharged. She tells you there is a **history in the family of a tumour 'syndrome'**, and one of her relatives died at a young age.

Which is the most likely underlying diagnosis >>> **MEN II b**

### Autoimmune Polyendocrinopathy / Polyglandular Syndrome (APS)

**Addison's disease** (autoimmune hypoadrenalism) is associated with other endocrine deficiencies in approximately 10% of patients.

There are 2 distinct types of autoimmune polyglandular syndrome (APS):

**APS type 1:** It is occasionally referred to as **Multiple Endocrine Deficiency Autoimmune Candidiasis (MEDAC)**. It is a very rare autosomal recessive disorder caused by mutation of AIRE1 gene on chromosome 21.

Features of APS type 1 (2 or more of the following):

- 1) **Primary hypoparathyroidism ( $\downarrow$ Ca):** in 90%
- 2) **Addison's disease:** in 60%
- 3) **Chronic mucocutaneous candidiasis** (typically **first** feature as young child).

These 3 major components of APS type 1 tend to present in the following chronological order of **candidiasis**, followed by **hypoparathyroidism**, followed by **adrenal insufficiency**.

EX: Pt with chronic mucocutaneous candidiasis and you suspect APS type I >>> check serum **Ca** and **Na & K**.

TTT: **Antifungals, Vit D, Calcium, Glucocorticoids** replacements.

**APS type 2:** (also referred to as **Schmidt's syndrome**) being **much** more common.

APS type 2 has a polygenic inheritance and is linked to HLA DR3/DR4.

Patients have:

- **Addison's disease** plus either:
  - Type 1 DM or
  - Autoimmune thyroid disease (Hypothyroidism)

**N.B:** Vitiligo, Myasthenia gravis, primary hypogonadism coeliac disease and pernicious anaemia can occur in both types of APS.

**N.B:** Primary hypoparathyroidism ( $\downarrow$ Ca) is usually the first endocrine manifestation of type 1 autoimmune polyendocrinopathy syndrome. The contrast to multiple endocrine neoplasia (MEN), where hyperparathyroidism ( $\uparrow$ Ca) is a common finding, should be noted.

**So**, Primary **HYPO**parathyroidism is usually the first endocrine manifestation of type I Autoimmune **POLY**endocrinopathy syndrome (APS).

While, in **MEN** >>>> **HYPER**parathyroidism is the commonest finding.

**EX:** Female pt 35 years old with hypothyroidism on thyroxin replacement, she has nausea, vomiting, lethargy, postural hypotension, vitiligo, anaemia Hb=10 gm/dl, Na=124, K=4.5. >>> This is APS type 2.

In this case, if delay in arranging short synacthen test was likely, Adrenal autoantibodies are likely to be positive in over 80% of cases.

It is medical emergency and should start **hydrocortisone IV**.

This anaemia may raise possibility of pernicious anaemia or coeliac disease.

**EX:** Young woman 20 years with type 1 diabetes with **weight loss**, **lethargy** and **reduced insulin requirements** with **increasing frequency of hypoglycaemic events** >>> points to a general increase in insulin sensitivity and with her history of autoimmune disease (type 1 diabetes), **hypoadrenalism** should be considered as the cause >>> Hence, a **short Synacthen test** is the most appropriate diagnostic test.

NB: Associated hypothyroidism would cause weight gain.

### Carcinoid syndrome

#### Carcinoid tumours:

- It is a neuroendocrine tumours, which originate from **enterochromaffin** cells of the **intestine**.
- Usually occurs when metastases are present in the liver and release serotonin (5-HT) into the systemic circulation which will cause **flushing**, **diarrhoea** and **bronchospasm**.
- They are indolent tumours secreting more than 20 different hormones, likely 5-HT, kinins, prostaglandins and other vasoactive substances are secreted.

- Most of cases with more than **95%** of patients with carcinoid tumour have **liver metastasis** at the time of diagnosis.
- The carcinoid syndrome **only** arises **when liver metastases are present** and the tumour products being metabolised by the liver by draining directly into the hepatic veins.
- May also occur with lung carcinoid as mediators are not 'cleared' by the liver.
- The most common **sites** for the **primary** tumour are the **appendix (40%)**, **terminal ileum (30%)**, **rectum (20%)**, and less commonly in the bronchus, ovary and testis.
- 80% of tumours greater than 2 cm in diameter will metastasize.
- **Very bad prognosis: average survival is 5-10 years from diagnosis**

**Features:**

- **Flushing** (often **earliest** symptom) in **75-90%** of cases, often provoked by alcohol.
- **Hypotension**
- Chronic **diarrhoea** (in > **70%**).
- **Bronchospasm** (in **25%**).
- **Right heart valvular stenosis e.g. tricuspid / pulmonary stenosis** is found in **50%** of cases and can lead to right-sided CHF like LL oedema (left heart can be affected in bronchial carcinoid).
- **Pellagra** can rarely develop as dietary tryptophan is diverted to serotonin by the tumour.
- Other molecules such as ACTH and GHRH may also be secreted resulting in, for example, Cushing's syndrome.

The <b>triad</b> of <b>facial flushing</b> , <b>chronic diarrhoea</b> and <b>cardiac</b> involvement represents more than <b>85%</b> of symptoms of carcinoid syndrome.
---

**Investigations:**

- **High 24-hour urinary 5-HIAA excretion:** (5-hydroxyindoleacetic acid) - is greater than 0.3 mmol.
- **Abdominal US:** to visualise the liver metastasis.
- **Chest and abdomen CT**
- Plasma chromogranin A y





\*Dopamine antagonist tests using metoclopramide may also be used in the investigation of hyperprolactinaemia. A normal response is at least a twofold rise in prolactin. A blunted prolactin response suggests a prolactinoma.

### **Prolactin and galactorrhoea**

Prolactin is secreted by the anterior pituitary gland with release being controlled by a wide variety of physiological factors.

**Dopamine** acts as the primary **prolactin** releasing **inhibitory** factor and hence dopamine agonists such as Bromocriptine may be used to control galactorrhoea.

**Prolactin is under continuous inhibition.**

It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia.

Prolactin is the unique amongst the pituitary hormones in being tonically (continuously) inhibited by the hypothalamus

Prolactin is important for **development of the fetal lung** in addition to its well-known role in lactation and breast development during pregnancy.

### **Features of excess prolactin:**

- Men: impotence, loss of libido, erectile dysfunction, galactorrhoea.
- Women: amenorrhoea, galactorrhoea, infertility

### **Classification of different causes of hyperprolactinaemia:**

#### **1) Hypothalamic stimulation:**

- **Primary hypothyroidism** (due to TRH stimulating prolactin release).
- **Adrenal insufficiency.**
- **Acromegaly:** 1/3 of patients

#### **2) Medications:** inhibit dopamine release, leading to reduced inhibition and therefore higher prolactin release.

- Anti-emetics: **Metoclopramide**, **Domperidone**
- Anti-ulcer agents: **H2 antagonists**, **omeprazole**
- Antihypertensive: **CCB (verapamil)**, **methyldopa**
- Psychotropic agents: **SSRI**, **TCA**
- Antipsychotics: **Risperidone**

- Neuroleptics: phenothiazines, haloperidol, sulpiride (Dogmatil®)
  - Opiates and opiate antagonists
  - Protease inhibitors
  - Combined oral contraceptive pills
- 3) **Neurogenic**: via autonomic nervous system.
- Chest wall injury
  - **B**reast stimulation
  - **B**reast feeding
- 4) **Physiological** causes: via oestrogen stimulation.
- Pregnancy, coitus
  - Exercise, sleep, stress
- 5) **Increased prolactin production**:
- Ovarian: polycystic ovarian syndrome
  - Pituitary tumours: adenomas (prolactinoma), hypothalamic stalk compression, hypophysitis
- 6) **Reduced prolactin elimination**:
- Renal failure
  - Hepatic insufficiency

The **first test** to do when seeing anyone with **hyperprolactinaemia** is to exclude **pregnancy**, as it is the **most common cause**.

**Hypothyroidism** is not an uncommon cause of hyperprolactinaemia and should be **part of the work up of all patients with an elevated prolactin and secondary amenorrhoea**.

**Significant hypothyroidism (TSH >10)** can result in raised levels of TRH (thyrotropin-releasing factor). This can act as prolactin-releasing factor and bind to the receptors, resulting in the release of prolactin. **TTT: Thyroxin**.

**Prolactin levels less than 1000** are most likely to be **drug related**.

**Microprolactinoma** is associated with levels of prolactin of **1,000-3,000 mU/L**.

In **Macroprolactinomas**, the prolactin concentration is **more than 3000 mU/L (with levels of prolactin of 3,000-6,000 or higher) (more than 6000 is suggestive of macroprolactinoma)**.

**MRI Pituitary:** **hypo**-intense lesion on **T1** weighted scanning.

**EX:** The 1500 mU/L is an option of an intermediate level between that seen with drug related hyperprolactinaemia and a microprolactinoma.

Hyperprolactinaemia is typical of pregnancy.

Microprolactinomas rarely expand during pregnancy (less than 1%) and the prolactin concentration is no guide to this and does not need to be measured.

Features that would give rise to suspicion of expansion would include field constriction and atypical headache symptoms. Severe frontal headache may suggest apoplexy for instance.

Headaches are common in pregnancy.

A Non-functioning pituitary tumour (**NFPT**) may cause **hyperprolactinaemia but of less than 2000 mU/L** through **local stalk compression** and may be associated with **low Estradiol, FSH, LH** and **high TSH** (dt it may occasionally secrete small amounts of TSH).

**MRI** brain is needed.

**Surgery** is the mainstay of therapy for **NFPT** as the tumour is highly **unlikely** to respond significantly to dopamine agonists or somatostatin.

After surgery patient should receive **replacement therapy** with **hydrocortisone** 10 mg am, 5 mg pm, **thyroxine** 150 µg daily (with follow up by free T4 not TSH) , **testosterone** 250 mg IM monthly and **growth hormone**.

**EX:** A 30-year-old female presents with galactorrhoea and an **elevated prolactin** of 1200 mU/L (50-450) and **low oestradiol** concentration of 100 pmol/L (130-450), **low FSH and LH** with raised TSH. Which of the following is the likely cause >>> **NFPT**.

N.B: Prolactinoma management >>> **Medical ttt** is almost always **first line even if visual field defects are present**.

**The dopamine agonists, Bromocriptine, and Cabergoline** (activate D2 receptors) reduce prolactin levels thereby allowing oestrogen levels to normalise. They are effective in most patients, but do normally need to continue long-term.

**Cabergoline** is an ergot-derived dopamine agonist, dose once or twice / week.

**Ropinirole** is non-ergot-derived dopamine agonists

**SE** of dopamine agonists: **Pericarditis, pericardial effusion, cardiac valve regurgitation and pulmonary hypertension.**

**Contraindications** to treatment are cardiac valve fibrosis and pulmonary fibrosis.

**EX:** Male pt. with erectile dysfunction, loss of libido and microprolactinaemia >>> start Cabergoline >>> Chest pain pericarditis >>> **Ropinirole** will be an appropriate alternative in this case.

Pituitary surgery is rarely required in prolactinomas and is generally reserved for patients intolerant of or resistant to dopamine agonist therapy.

The main indication for surgery are tumours resistant to dopamine agonists.

Outcomes for **surgery** are generally **poor** with high risk of **recurrence** ☹

Many women with a microprolactinoma can be maintained on dopamine agonists without the need to progress to surgery which itself carries associated morbidity.

As such there is no need to stop therapy or progress to surgery before trying for a child, indeed stopping therapy will reduce the chance of ovulation.

**Combined oral contraceptives can lead to mild rises in serum prolactin**, and therefore should only be used with caution in patients with prolactinomas.

There is no evidence that bromocriptine is teratogenic from available data on use in pregnancy. There are less data on cabergoline and so this is not recommended.

**Once pregnancy is established, bromocriptine** is not necessarily required, and so most physicians recommend **stopping** it for the duration.

There is no evidence that bromocriptine is required to be continued throughout the pregnancy.

**EX:** Female patient with inability to achieve pregnancy with pituitary microadenoma on bromocriptine and want to get pregnant >>> She should know that **within a few months** menstrual cycles are likely to return and that pregnancy has a much higher probability and so she should **stop** her **bromocriptine** once she knows she is pregnant (i.e. as soon as she has a positive pregnancy test) (**NOT** prior to trying to get pregnant).

**EX:** Any patient has a **co-incidentally noted pituitary tumour** and has **no** endocrine symptoms (i.e. **NORMAL OF ALL:** normal visual field, normal thyroid, normal synacten test, normal testosterone/oestrogen, FSH, LH) >>> so **reassurance, observation and repeat scanning.**

## **Gynaecomastia**

Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an **increased oestrogen: androgen ratio**.

It results from an imbalance of oestrogens and androgens in the male patient.

It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia.

The incidence of gynaecomastia typically occurs at 3 distinct periods of life:

- Neonatal - due to maternal oestrogens crossing the placenta.
- Puberty - low testosterone and dihydrotestosterone (DHT) during puberty.
- Adult life - typically 50-80-years-old, which may be due to primary testicular failure, obesity or alcohol excess.

Causes of gynaecomastia:

- Physiological: normal in neonatal, puberty and elderly.
- Syndromes with androgen deficiency: Kallman's, Klinefelter's
- Testicular failure: e.g. mumps
- Testicular cancer e.g. seminoma secreting **hCG**
- Ectopic tumour secretion
- **Liver cirrhosis** (only 8% of cases)
- **Renal failure: Haemodialysis**
- **Hyperthyroidism** (Gynaecomastia is seen in up to a third of men with thyrotoxicosis, but is not a feature of hypothyroidism).
- **Drugs** related gynaecomastia (it accounts **10-25%** of cases): see below

Drug causes of gynaecomastia:

- **Spironolactone** (most common drug cause)
- **Cimetidine**, also **omeprazole**
- Digoxin
- Finasteride
- Gonadorelin analogues e.g. Goserelin (Zoladex ®), buserelin: It is used in the treatment of advanced prostate cancer.
- Oestrogens, anabolic steroids
- Cannabis

Very rare drug causes of gynaecomastia:

- TCA (e.g. Amitriptyline)
- Isoniazid
- Calcium channel blockers
- Methyldopa
- Busulfan
- Heroin

**N.B:** Tamoxifen may be used to treat gynaecomastia.

**NB:** Neither hyperprolactinaemia nor hypopituitarism disturb this ratio and are rarely associated with gynaecomastia (i.e. prolactinoma not cause gynaecomastia).

**NB: Spironolactone** causes gynaecomastia by several mechanisms:

- 1) It can block androgen production by inhibiting enzymes in the testosterone synthetic pathway, and
- 2) It can also block receptor binding of testosterone and dihydrotestosterone.
- 3) It displaces oestradiol from sex hormone binding globulin (SHBG), which increases free oestrogen levels.

**NB:** The mechanism of digoxin-induced gynaecomastia is thought to be a direct action at oestrogen receptors.

**N.B:**

- Primary hypothyroidism >> ↑ Prolactin
- Hyperthyroidism >> Gynaecomastia

## **Amenorrhoea**

It may be divided into **primary** (failure to start menses by the age of **16** years) or **secondary** (cessation of established, regular menstruation for 6 months or longer).

### **Causes of primary amenorrhoea (5):**

- 1) **Turner's syndrome:** Hypergonadotrophic hypogonadism, short stature.
- 2) **Kallmann's syndrome** (hypogonadotrophic hypogonadism).
- 3) **Testicular feminisation syndrome:** good breast development in the absence of secondary sexual hair, with a history of hernias as a child (undescended testes). The vagina is blind ended, and there are no ovaries.

- 4) **Congenital adrenal hyperplasia**
- 5) Congenital malformations of the **genital** tract.
- 6) **Anorexia nervosa** (hypogonadotrophic hypogonadism with mild ↑ prolactin).

**Causes of secondary amenorrhoea (after excluding pregnancy):**

- 1) Hypothalamic amenorrhoea (e.g. Stress, excessive exercise)
- 2) Polycystic ovarian syndrome (PCOS)
- 3) Hyperprolactinaemia
- 4) Premature ovarian failure
- 5) Thyrotoxicosis
- 6) Hypothyroidism may also cause amenorrhoea
- 7) Autoimmune hepatitis.

**Initial investigations:**

- 1) Exclude pregnancy with urinary or serum βHCG.
- 2) Gonadotrophins (FSH): low levels indicate a hypothalamic cause whereas raised levels suggest an ovarian problem (e.g. premature ovarian failure).
- 3) Prolactin.
- 4) Androgen levels: raised levels may be seen in PCOS.
- 5) Oestradiol.
- 6) Thyroid function tests.

**NB:** In pregnancy: ↑ **Estradiol**, with **suppressed LH and FSH**, and ↑ **prolactin**

**NB:** Pregnancy would be associated with elevated oestradiol concentrations.

**Polycystic ovarian syndrome (PCOS)**

Polycystic ovary syndrome (PCOS) is a complex condition of ovarian dysfunction, it is extremely common, thought to affect between 5-20% of women of reproductive age.

PCOS is the most common cause of hyperandrogenism in women of reproductive age.

Management is complicated and problem based partly because the aetiology of PCOS is not fully understood.

Both hyperinsulinaemia and high levels of LH are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

PCOs is associated with a **raised LH: FSH ratio >2**, with **insulin resistance** and **hyperandrogenism** as evidenced by **raised androstenedione**, **raised Serum dehydroepiandrosterone sulphate (DHEAS)** and **slightly raised or normal testosterone but raised free androgen index**.

**Serum sex hormone binding globulin (SHBG)** is **lower** in PCOS. The reasons include that androgens reduce the globulin production, whereas oestrogen promotes production. It is a protein for transport of hormones in the blood.

Elevated prolactin, although a feature of PCOs, is not specific of the diagnosis and may suggest microprolactinoma.

Although insulin resistance is a feature of PCOs, a raised insulin concentration is rather irrelevant and no one would measure this in clinical practice. It is often elevated in association with testosterone secreting tumours.

The Rotterdam International Consensus Group (2003) described PCOS as a syndrome of ovarian dysfunction, characterised by hyperandrogenism and polycystic ovaries. They recommended that diagnosis be made if **two** of the following three criteria were met:

- 1) Oligomenorrhoea or anovulation.
- 2) Clinical and/or biochemical evidence of hyperandrogenism.
- 3) Polycystic ovaries on ultrasonography: multiple peripheral follicles with ovarian volume greater than 10 ml.

Other diseases which can cause similar symptoms, such as androgen secreting tumours, Cushing's syndrome and congenital adrenal hyperplasia must also be excluded.

### **Features:**

- Subfertility and infertility
- Menstrual disturbances (Irregular heavy periods) : oligomenorrhea and amenorrhoea
- Male pattern Hirsutism, acne (due to hyperandrogenism)
- Obesity
- **Acanthosis nigricans** (due to **insulin resistance**)
- Clitoromegaly is seen occasionally in PCOS but is normally associated with very high androgen levels. If clitoromegaly is found then further investigations to exclude an ovarian or adrenal androgen secreting tumour are required.



**Investigations:**

- Pelvic ultrasound: multiple cysts on the ovaries which is the **most consistent feature** of PCOD: the presence of at least 8 follicular cysts of less than 10 mm and increased ovarian stroma.
- FSH, LH, prolactin, TSH, and testosterone are useful investigations:
- Raised LH: FSH ratio > 2 is **a 'classical' feature** but is no longer thought to be useful in diagnosis.
- Prolactin may be normal or mildly elevated.
- **Testosterone may be normal or mildly elevated - however, if markedly raised consider other causes.**
- Check for impaired glucose tolerance.
- Typically in PCOS, **Oestradiol is normal or elevated** and a low oestradiol would be in keeping with Cushing's.

**N.B:** In PCOD >>> multiple ovarian cysts by US are the most consistent feature, however Raised LH: FSH ratio is a 'classical' feature but is no longer thought to be useful in diagnosis.

It is recognised however that LH: FSH ratio is not always predictive of the presence of polycystic ovaries, **so for this reason abdominal ultrasound scan is the investigation of choice.**

**EX:** A 39-year-old woman comes to the clinic complaining of **excessive hairiness** and problems with **acne**. She also reports **increased libido** over the past few months. **Testosterone** is **8.9 nmol/L** (N <2.5).

The most likely underlying diagnosis is >>> **Androgen secreting tumour >>> Abdominal ultrasound, CT or MRI** to elucidate whether an adrenal or ovarian tumour is the underlying cause.

The key here is the testosterone level, which is **more than 3 times the upper limit of normal**.

**Female patient with hirsutism, irregular periods and HTN:**

- 1) **PCOD:** so LH/FSH ratio is the 1<sup>st</sup> D.D of this patient.
- 2) **Cushing's syndrome:** the 2<sup>nd</sup> D.D.: ODST or 24 hrs urinary free cortisol.
- 3) **Cushing's disease:** by high-dose dexamethasone suppression test, only used if the ODST was previously positively suppressed. Then **plasma ACTH** and **MRI**

**pituitary** are performed to localise the cause of the cortisol production once positive suppression test.

### **DD for PCO:**

- Cushing,
- Congenital adrenal hyperplasia

### **Polycystic ovarian syndrome (PCOS): management**

#### **General:**

- **Weight reduction** if appropriate:
  - Weight loss is the **gold standard** ttt of PCOD.
  - It decrease insulin resistance, ↑ SHBG and ↓ free androgens level and improve ovulation.
  - A 5% weight loss is said to result in 40% improvement in hirsutism.
- If a women requires contraception then a combined oral contraceptive pill (COCP) may help regulate her cycle, induce a monthly bleed and reduces hyperandrogenism (**Dianette ®**)

#### **Hirsutism and acne:**

- A **Combined OCP** may be used help manage hirsutism. Possible options include a third generation COC which has fewer androgenic effects or **Co-Cyprindiol (Cyproterone acetate + Ethinylestradiol 2000/35 mg) (Dianette 35 ®)** which has an anti-androgen action. Both of these types of COC may carry an increased risk of venous thromboembolism.
- If doesn't respond to COC then **topical eflornithine** may be tried.
- **Anti- androgens like: Spironolactone, flutamide and finasteride** may be used under specialist supervision.
- **Metformin.**

#### **Infertility:**

- **Weight reduction** if appropriate.
- The management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether **metformin**, **clomifene** or a combination should be used to stimulate ovulation.

- A 2007 trial published in the New England Journal of Medicine suggested **clomifene was the most effective treatment**. There is a potential risk of multiple pregnancies with anti-oestrogen therapies such as clomifene.
- The RCOG published an opinion paper in 2008 and concluded that on current evidence metformin is not a first line treatment of choice in the management of PCOS.
- Metformin is also used, either combined with clomifene or alone, particularly in patients who are obese as it increases peripheral insulin sensitivity.
- Metformin has been shown to increase the rate of conception in PCOs through improved insulin sensitivity and helps to restore ovulatory functions (although studies have not been powered to show a significant impact on pregnancy outcome).
- Gonadotrophins.
- Pioglitazone as an insulin sensitizer improves insulin sensitivity and restores ovulatory function.

**Infertility in PCOS >>> Clomifene is superior to metformin**

Clomifene: works by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion.

### Congenital adrenal hyperplasia (CAH)

CAH is caused by **21-hydroxylase deficiency** in around **95%** of cases.

This results in **cortisol deficiency**, **aldosterone deficiency** and **androgen excess**.

Due to the enzyme block, cortisol cannot be made effectively and androgens are made instead.

The **classical** form has its onset in infancy or childhood.

The **non-classical "mild"** form are characterised by milder enzyme dysfunction, and therefore usually only manifest **later** in adolescence or adulthood. **17-OH progesterone** is **elevated** because of the enzyme deficiency.

**Urinary 17-ketosteroid levels** (androgen metabolites) are **elevated** in the condition.

The clinical presentation may be **indistinguishable** from (**PCO**) polycystic ovarian syndrome, with **hirsutism** being a dominant feature.

**Short Synacthen test (ACTH stimulation test) with measurement of 17-OH progesterone (17-OHP):** can help to **distinguish** between PCOS and non-classical CAH: N-CAH due to 21-hydroxylase deficiency is diagnosed with the ACTH-stimulated **17-OHP** levels are **more than 30 nmol/L** (although this value varies with the assay used). N-CAH is not characterised by cortisol insufficiency, and as such glucocorticoids are rarely indicated.

**TTT:**

- If the main concern is infertility, **ovulation induction** is the treatment of choice.
- If hirsutism is the presenting problem then **anti-androgens** (such as **flutamide 250 mg cap**) should be used to treat hirsutism, but glucocorticoids are generally **not** required.
- The treatment of CAH is **the lowest dose of glucocorticoid (Hydrocortisone)** that suppresses (not totally) adrenal androgens, whilst maintaining normal growth and weight gain.

**NB:** Hydrocortisone has a relatively **short half-life** and must therefore be administered **twice daily** whilst the **preferred** mode of glucocorticoid replacement in **children** is hydrocortisone **as it minimises growth suppression**.

**NB:** Efficacy of treatment of CAH is best **monitored** by **17-OH progesterone** and **androstenedione** levels.

**EX:** An 18-year-old woman comes to the clinic complaining of acne and hirsutism, secondary amenorrhoea. She has no medical history of note and her only medication is the oral contraceptive pill. Lab: hypogonadotrophic hypogonadism (↓Estradiol, ↓FSH, ↓LH) >>> **CAH** The **non-classical "mild"** form with elevated level of ↑ **17-OH progesterone**

**EX:** Young female with hirsutism >>> check (5):

- FSH, LH, oestradiol
- Testosterone
- Androstenedione
- Dehydroepiandrosterone sulphate (DHEAS)
- 17-hydroxyprogesterone

### Androgen insensitivity syndrome (AIS)

Androgen insensitivity syndrome is the new term for **testicular feminisation syndrome**.

Androgen insensitivity syndrome is an **X-linked recessive** condition due to end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype.

الشكل بنت وامورة جدا وبدون شعر ... ولكن الجينات راجل

Features:

- 'Primary amenorrhoea'.
- Undescended testes causing groin swellings.
- Normal breast development may occur as a result of conversion of testosterone to oestradiol.
- Normal external genitalia they appear female.

Diagnosis:

- 1) Buccal smear or chromosomal analysis to reveal 46XY genotype.
- 2) The serum testosterone is in the male range.

Management:

- 1) **Counselling** - raise child as **female**
- 2) **Bilateral orchiectomy** (there is increased risk of testicular cancer due to undescended testes).
- 3) **Oestrogen** therapy: **Diethyl-Stilboestrol (DES)** is a synthetic nonsteroidal estrogen has been associated with the induction of latent tumours and with influencing sexual behaviour, but is not associated with abnormalities of sexual identity.

EX: A 16-year-old **female** patient is referred with **primary amenorrhoea**. Investigations reveal a 46 XY karyotype: **Androgen insensitivity syndrome**

**N.B: Summary**

<b>Disorder</b>	<b>Investigation of choice</b>
Cushing's	Overnight Dexamethasone Suppression Test Or 24 hours urinary free cortisol
Cushing's vs. Pseudo-Cushing's	Insulin Stress Test
Addison's	Short Synacthen Test
Phaeochromocytoma	Three 24 Hrs Urinary Catecholamines
Acromegaly	OGTT (Oral Glucose Tolerance Test)
Carcinoid syndrome	Urinary 5-HIAAA

# Haematology



**Iron deficiency anaemia (IDA)**

Features:

- 1) Angular stomatitis
- 2) Atrophic glossitis
- 3) Post-cricoid webs
- 4) Koilonychia

Blood film:

- **Target cells**
- **'Pencil' poikilocytes**
- If combined with B12/folate deficiency a **'dimorphic' film** occurs with mixed microcytic and macrocytic cells

**Hypoferritinaemia** confirms IDA and is the preferred screening test.

<b>IDF &gt;&gt;&gt; check serum ferritin</b>
--

A microcytic anaemia in a female should raise the possibility of either gastrointestinal blood loss or menorrhagia.

Absorption of oral iron is improved by **vitamin C ascorbic acid**.

Ferrous **sulphate** has more elemental iron by mass than the same dose of ferrous gluconate

Iron is absorbed in the **upper small intestine**.

**Parenteral** iron acts **no faster than oral iron**. It is indicated when **oral iron** cannot be **tolerated** or is **not absorbed**.

**Sustained release** preparations may improve **tolerance** of oral iron but do not aid absorption.

**Iron metabolism****Absorption:**

- **Upper small intestine.**
- About 10% of dietary iron absorbed.
- **Fe<sup>2+</sup> (ferrous iron)** much better absorbed than Fe<sup>3+</sup> (ferric iron).



- Absorption is regulated according to body's need.
- **Increased** by **vitamin C** and **gastric acid**.
- **Decreased** by PPIs, tetracycline, gastric achlorhydia, tannin (in tea).
- From an intake of approximately 6 mg/1000 kcal of dietary iron **only 15% is bioavailable**.

**Distribution in body:**

- **Total body iron = 4g** (2500 mg in the RBCs, 500 mg in liver, 500 mg in macrophages and about 500 mg in muscle). Approximately **4 mg** of iron circulate within the plasma. **So approximately 0.1% of body iron circulates in the plasma.**
- **Haemoglobin = 70%**
- Ferritin and hemosiderin = 25%
- Myoglobin = 4%
- Plasma iron = 0.1%

The majority of iron found in the body is in **Haemoglobin** about **70%**.

**Transport:** Carried in **plasma** as **Fe<sup>3+</sup>** bound to **transferrin**.

**Storage:** Stored as **ferritin** in **tissues**. It is the plasma protein responsible for binding iron, is an acute phase reactant protein which is **increased** in inflammatory conditions following surgery.

**Excretion:** Lost via intestinal tract following desquamation. The majority of iron contained within the RBCs is metabolised and re-utilised but 1 mg per day is lost through the gut.

**Transferrin** is a glycoprotein responsible for internal iron exchange and the content within **mucosal cells** is naturally **high** in **haemochromatosis** with **high iron store saturation**.

Fe<sup>2+</sup> (ferrous iron) is oxidised to Fe<sup>3+</sup> (ferric iron) by caeruloplasmin to bind to **transferrin** which is about **one third saturated** with iron.

In absence of anaemia, **transferrin** is about **33% saturated** with iron.

Iron (Fe 3+) is carried in the blood bound to transferrin.

**Pregnancy** and the **oral contraceptive pill (OCP)** both **increase transferrin**.

The **transferrin saturation %** (plasma iron /TIBC x 100) is used as a measure of iron **stores**. A value **below 16%** is indicative of **iron deficiency**.

In **iron deficiency** >>> **low** serum Fe, **rise** TIBC, **rise** the transferrin level.

In **iron overload** >>> **fall** in both TIBC and transferrin.

In **haemochromatosis** >>> **increased** in **Transferrin saturation%**.

#### **Indications for IV iron include:**

- 1) Patients requiring iron supplementation who are **unable to tolerate** compounds given orally, or
- 2) Patients who **fail to comply** with prescriptions for oral iron supplementation.
- 3) Patients with **gastro-intestinal disorders**, such as inflammatory bowel disease (ulcerative colitis and Crohn's disease), in which symptoms may be aggravated by oral iron therapy, or
- 4) Patients who are unable to maintain acceptable iron levels during treatment with **haemodialysis**.

It is considered best practice to administer **1000 mg** of **low** molecular weight iron dextran in **250 mL of normal saline in 1 hour without premedication**; a **test dose of 10 to 25 mg is infused over 3 to 5 minutes** prior to the first infusion.

If no acute reaction is observed, the remaining solution is infused over the balance of 1 hour.

For **those** with a history of drug allergies or hypersensitivity, **125 mg of methylprednisolone is infused prior to the test dose**.

#### **Thalassaemia**

It is a haemoglobinopathy resulting from defective synthesis of globin chains required for Hb synthesis.

Each copy of **chromosome 16** has two genes for the **alpha globin** subunit (**four** in total).

And each copy of **chromosome 11** has one genes for the **beta globin** subunit (**two** in total).

- Adult Hb= **HbA ( $\alpha_2\beta_2$ )** (Normal > **95%**)
- Second adult Hb= **HbA2 ( $\alpha_2\beta_2$ )** (Normal < **3.5%**),
- Fetal Hb=**HbF ( $\alpha_2\gamma_2$ )** (Normal < **1.5%**)

**Alpha-thalassaemia:**

Alpha-thalassaemia is due to a deficiency of alpha chains in haemoglobin.

**2 separate alpha-globulin genes** are located on each **chromosome 16**.

Clinical severity depends on the number of alpha chains present:

- 1) If 1 (aa/-a) or 2 (aa/--) alpha chains are absent then the blood picture would be hypochromic and microcytic, but the Hb level would be typically normal.
- 2) Loss of 3 alpha chains results in a hypochromic microcytic anaemia with splenomegaly. This is known as **Hb H** disease, thalassemia intermedia.
- 3) If all 4 alpha chains absent (--/--) (i.e. homozygote) then death in utero (hydrops fetalis, Bart's hydrops, gamma 4 tetramer).

I.e. we can say that in  $\alpha$ -thalassemia:

- 1) 1 gene deletion (aa/-a): **Silent carrier**.
- 2) 2 gene deletion (aa/--):  **$\alpha$ -thalassaemia trait** ( $\downarrow$  HbA2).
- 3) 3 gene deletion (a/--): **HbH ( $\beta_4$ )**: moderate anaemia, splenomegaly.
- 4) 4 gene deletion (--/--): **Hydrops fetalis, Bart's Hb ( $\gamma_4$ )**.

**Beta-thalassaemia:**

Beta-thalassaemias are due to mutations in the HbB gene on **chromosome 11**, also inherited in an **autosomal recessive** fashion.

The severity of the disease depends on the nature of the mutation.

Mutations are characterized as:

- $\beta^0$  or  $\beta$  thalassaemia major: if they prevent any formation of  $\beta$  chains, which is the most severe form of  $\beta$  thalassemia.
- $\beta^+$  or  **$\beta$  thalassaemia intermedia**: if they allow some  $\beta$  chain formation to occur.

In either case there is relative excess of  $\alpha$  chains, but these don't form tetramers. Rather they bind to the RBC membranes producing membrane damage and at high concentrations they form toxic aggregates.

- 1) 1 gene deletion:  **$\beta$  thalassaemia minor / trait**: (mild microcytic hypochromic anaemia, **marked microcytosis (very low MCV)**,  $\uparrow$ HbA2  $> 3.5\%$ , it is usually **asymptomatic**. Microcytosis is characteristically **disproportionate** to the anaemia. (i.e. the Microcytosis is disproportionately with very low MCV for the near normal Hb level  $>9$ ).
- 2) 2 gene depletion ( $\beta^0\beta^0$ ):  **$\beta$  thalassaemia major**: anaemia when HbF tries to convert to HbA during first year of life, extramedullary haemopoiesis with

hepatosplenomegaly and bone marrow expansion, “hair on end” appearance of bone.

The terms thalassemia minor, intermedia & major do not pertain to  $\alpha$ - or  $\beta$ -thalassemia rather they describe whether the patient is asymptomatic (minor), transfusion dependant (major) or in between (intermedia).

**Ex:** 23-year-old **Chinese** woman presents with lethargy, Hb 10.5%, MCV 60 fl, Blood film: Microcytic hypochromic RBCs, marked anisocytosis and basophilic stippling noted, HbA2 = 4%.

What is the most likely diagnosis? >> **Beta-thalassemia trait.**

Microcytic anaemia would immediately raise the suspicion of iron deficiency perhaps from GIT or menstrual blood loss. However, the **MCV here is disproportionately low**. This combined with a **raised HbA2** makes the diagnosis of **beta-thalassemia trait** the most likely diagnosis.

**Note that in cases of severe iron deficiency anaemia the HbA2 may be normal in thalassemia minor.**

**EX:** Pt 44 years old, Hb 9, MCV 60, FOB +ve, HbA2 is normal >>> **Co-existing B-Thalassemia minor and iron deficiency anaemia**, and need to rule out GIT blood loss.

**Beta thalassemia major** is characterised by **anaemia**, **splenomegaly**, **bone deformities** and **early death** if not treated appropriately.

A **transfusion programme with iron chelation** is the best initial approach.

The transfusional iron overload, which can be managed with iron chelation, both IV/SC (desferrioxamine) and/or oral (deferasirox).

The next of kin should be offered screening >> the parents and other siblings should be **screened by genetic testing**.

**Desferrioxamine** binds iron but needs to be given for 8-12 hours a day for 5-7 days per week, so is a major undertaking for the patient. SE: high frequency deafness, retinopathy and Yersinia infection.

**Delta thalassaemia:**

As well as alpha and beta chains being present in Hb, about 3% of adult Hb is made of alpha and delta chains.

Just as with Beta-thalassaemia, mutations can occur which affect the ability of this gene to produce delta chains.

Thalassemia can co-exist with other haemoglobinopathies. The most common of these are:

- **HbE/thalassaemia:** common in Cambodia, Thailand, and parts of India: clinically similar to  $\beta$  thalassaemia major or thalassaemia intermedia.
- **HbS/thalassaemia:** common in African and Mediterranean populations: clinically similar to sickle cell anaemia with additional feature of splenomegaly.
- **HbC/thalassaemia:** common in African and Mediterranean populations:
  - **HbC/ $\beta^0$  thalassaemia:** causes moderate to severe haemolytic anaemia with splenomegaly.
  - **HbC/ $\beta^+$  thalassaemia:** produce a milder disease.

**Macrocytic anaemia**

Macrocytic anaemia can be divided into causes associated with a Megaloblastic bone marrow and those with a normoblastic bone marrow.

Megaloblastic causes	Normoblastic causes
<ul style="list-style-type: none"> <li>• <b>Vitamin B12 deficiency</b></li> <li>• <b>Folate deficiency</b></li> </ul>	<ul style="list-style-type: none"> <li>• Alcohol</li> <li>• Liver disease</li> <li>• Hypothyroidism</li> <li>• Pregnancy</li> <li>• Reticulocytosis</li> <li>• Myelodysplasia</li> <li>• Drugs: cytotoxics (methotrexate &amp; azathioprine)</li> </ul>

**Vitamin B12 deficiency**

Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system.

It is absorbed after **binding** to **intrinsic factor (IF)** (secreted from **parietal** cells in the stomach) and is **actively absorbed in the terminal ileum**.

A small amount of Vit. B12 is passively absorbed without being bound to IF.

Causes of vitamin B12 deficiency:

- 1) **Dietary** deficiency of Vit B12: like **vegetarians**, Vit B12 is only found in foods of animal origin e.g. meat, fish and eggs.
- 2) Pernicious anaemia
- 3) Post gastrectomy
- 4) Disorders of terminal ileum (site of absorption): Crohn's, blind-loop etc.

Features of vitamin B12 deficiency:

- Macrocytic anaemia
- Sore tongue and mouth
- Neuropsychiatric symptoms: e.g. Ataxia, Mood disturbances

**Investigations for the pernicious anaemia:**

- **Anti-gastric parietal cell Ab** (most common found in 90% of cases but less specific).
- **Anti-Intrinsic factor Ab** (found in 50% but specific for pernicious anaemia).
- Macrocytic anaemia (↑ MCV)
- Pancytopenia (with ↓ TLC , ↓ PLt)
- ↑LDH may be raised due to ineffective erythropoiesis.
- ↓ serum vitamin B12
- ↓ serum folic acid
- Hypersegmented polymorphs on films, Megakaryocytes in bone marrow.
- Schilling test:
  - Radiolabelled Vit B12 is give on two occasion.
  - First on its own as I.M
  - Second with oral intrinsic factor
  - Measure urine B12

A **normal serum gastrin excludes** pernicious anaemia (N < 55 pmol/l).

**Management:**

- If no neurological involvement **1 mg of IM Hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months.**
- If a patient has deficient in both vitamin B12 and folic acid then it is important to treat the **B12 deficiency first** to avoid precipitating subacute combined degeneration (SCD) of the cord.

**Pure Red Cell Aplasia (PRCA)**

It is diagnosed when: **(4)**

- 1) There is unexplained anaemia.
- 2) + Reticulocytopenia
- 3) + Complete absence of red cell precursors in the bone marrow,
- 4) + With preservation of other cell lines.

It occurs either **spontaneously** or **associated with:**

- Thymoma
- Autoimmune
- Lymphoproliferative disorder

Treatment:

- Immunosuppressive: Cyclosporine.
- Erythropoietin (but check firstly the Anti- Erythropoietin Abs).

**EX:** Pt with ESRD on dialysis and EPO, she is tired and has anaemia Hb 5 gm%, although on EPO >>> ? **Pure red cell aplasia**, confirm by **bone marrow** >>> absent erythropoiesis, normal myeloid, plentiful megakaryocytes and no infiltrates >>> TTT: **withdraw EPO** with subsequent falling of antibody levels.

**Haemolytic anaemias: by site (Intra/Extra Vascular)**

In intravascular haemolysis free Hb is released which binds to haptoglobin.

As haptoglobin becomes saturated, Hb binds to albumin forming methaemalbumin (detected by Schumm's test).

Free Hb is excreted in the urine as haemoglobinuria, haemosiderinuria.

Intravascular haemolysis: causes:	Extravascular haemolysis: causes (usually abnormal RBCs shape)
<ul style="list-style-type: none"> <li>➤ Mismatched blood transfusion.</li> <li>➤ Red cell fragmentation: heart valves, HUS, TTP, and DIC.</li> <li>➤ PNH</li> <li>➤ <u>C</u>old AIHA</li> <li>➤ <u>G</u>6PD deficiency* (also Extra)</li> </ul>	<ul style="list-style-type: none"> <li>➤ <u>H</u>aemoglobinopathies: sickle cell, thalassemia.</li> <li>➤ <u>H</u>ereditary spherocytosis</li> <li>➤ <u>H</u>aemolytic disease of newborn.</li> <li>➤ <u>W</u>arm AIHA.</li> </ul>

\*N.B: Strictly speaking there is an element of extravascular haemolysis in G6PD as well, although it is usually classified as an intravascular cause.

### Autoimmune haemolytic anaemia (AIHA)

It may be divided in to 'warm' and 'cold' types, according to at what temperature the antibodies best cause haemolysis.

It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection or drugs.

AIHA is characterised by a **positive direct antiglobulin test (AGT)** (Direct Coombs' test).

#### **Cold AIHA:**

The antibody in cold AIHA is usually **IgM** and causes haemolysis best at **4° C**. Haemolysis is mediated by complement and is more commonly **intravascular**.

Features may include symptoms of Raynaud's and acrocynaosis.

Patients respond less well to steroids.

Causes of cold AIHA:

- 1) **Primary:** idiopathic cold haemagglutinin disease
- 2) **Secondary** to:
  - Neoplasia: e.g. lymphoma
  - Infections: e.g. *Mycoplasma pneumoniae*, EBV



**Warm AIHA:**

In warm AIHA the antibody (usually **IgG**) causes haemolysis best at body temperature and haemolysis tends to occur in **extravascular** sites, for example in the liver and spleen, so measurement of haemoglobinaemia/ haemoglobinuria/ hemosiderin will be negative.

Management options include steroids, immunosuppression and splenectomy.

**Blood transfusion** can be life-saving until **immunosuppression** can take effect.

The bone marrow respond by increasing RBCs production, which will be evident in peripheral blood by increase in the **reticulocytes**, immature RBCs, which will have **high MCV**.

All patients with active haemolysis are at risk of acquiring folate deficiency due to increased metabolic demands and all should receive **folic acid** replacement therapy.

Causes of warm AIHA:

- 1) Autoimmune disease: e.g. **RA**, **SLE**\*
- 2) Neoplasia: e.g. lymphoma, **CLL**
- 3) Drugs:
  - E.g. **Penicillin**, **penicillin derivatives**, **Cephalosporins**, Methyldopa, levodopa, NSAIDs and Quinidine.
  - TTT: stop the offending drug ± short course of oral prednisolone.

\*SLE can rarely be associated with a mixed-type AIHA.

**EX:** A 32-year-old man was prescribed an oral antibiotic for a UTI, 2 days later he noticed that his urine was increasingly dark in colour with tinge of jaundice.

Lab: ↓Hb= 8.5 g/l. ↑Reticulocytes= 147 ×10<sup>9</sup>/L (N= 25-85), Blood film: marked anisopoikilocytosis and bite cells.

What is the most likely diagnosis >>> AIHA

**Paroxysmal cold haemoglobinuria (PCH)** is a **rare** type of autoimmune haemolytic anaemia (AIHA) occurring primarily in **children/adolescent**.

The classic symptom of PCH is a sudden onset of haemoglobinuria following **exposure to cold, even for a few minutes**.

Symptoms may occur minutes to hours following exposure to cold.

The **direct agglutination test (DAT)** (**Coomb's test**) is usually **negative**.

Haemoglobinuria is not always present because in some persons with PCH the autoantibody level is not high enough to cause intravascular haemolysis.

PCH is usually of abrupt onset in the setting of an infectious disease.

### **Paroxysmal nocturnal haemoglobinuria (PNH)**

It is an acquired disorder leading to **haemolysis** (mainly **intravascular**) of haematological cells.

It is thought to be caused by increased sensitivity of cell membranes to complement due to a lack of glycoprotein glycosyl-phosphatidylinositol (GPI).

PNH is a disorder in which the cells **lack surface proteins** such as Decay Accelerating Factor **CD 55 (DAF)** and Membrane Inhibitor of Reactive Lysis **CD 59 (MIRL)**.

As a result, the RBCs are sensitive to destruction by complement and platelets are activated, these cause **intravascular haemolysis with dark morning urine** and **recurrent thrombotic events**.

Patients are at increased risk of **aplastic anaemia** and **leukopenia**.

Patients are more prone to **venous thrombosis (DVT/PE, Budd-Chiari Syndrome)**.

Patients have **pancytopenia** and have a **pro-thrombotic** tendency with DVTs.

**Abdominal pain** is a common symptom and may be due to small mesenteric vein thrombi.

**Haemolysis** is **intermittent** - classically **nocturnal** - giving the **morning** urine a typical **dark** appearance.

Pathophysiology: (**Post-translational modification**)

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane.
- Complement-regulating surface proteins, e.g. decay-accelerating factor (DAF), are not properly bound to the cell membrane due a lack of GPI.
- **Thrombosis** is thought to be caused by a **lack of CD59** on platelet membranes predisposing to platelet aggregation.

Features:

- 1) **Haemolytic anaemia**
- 2) **Pancytopenia** may be present: Red blood cells, white blood cells, platelets or stem cells may be affected.
- 3) **Aplastic anaemia** may develop in some patients
- 4) **Haemoglobinuria**: classically dark-coloured urine in the morning, (although has been shown to occur throughout the day), urine is +ve for blood (haemoglobin) but no red cells.
- 5) **Thrombosis** e.g. Budd-Chiari syndrome, DVT/PE.

PNH = Intravascular haemolysis + Thrombosis + Pancytopenia

Diagnosis:

- **Flow cytometry** of blood to detect **low** levels of **CD55 and CD59** has now replaced Ham's test as the gold standard investigation in PNH.
- Positive Ham's test (sucrose lysis test): acid-induced haemolysis (normal red cells would not), it has low sensitivity.

The gold standard investigation in PNH >> **Flow cytometry** of blood to detect **low** levels of **CD55 and CD59.**

Management:

- 1) Blood product replacement
- 2) **Anticoagulation**
- 3) **Eculizumab**, a monoclonal antibody directed against terminal protein C5, is currently being trialled and is showing promise in reducing intravascular haemolysis
- 4) Stem cell transplantation.

**EX:** Male pt. 33 years old, has breathlessness for 3 months, pallor, DVT on warfarin for 6 months, dark urine. Lab: Hb 6, TLC 3, PLT 70, ↑ RTX and urine + ve blood +++ >>> **PNH.**

**EX:** Male Pt 33 years old with recurrent LL DVT, abdominal pain, jaundice and pancytopenia >>> **PNH.**

**EX:** Female 33 years old, severe fatigue, dark urine, severe abdominal pain, abdominal distension with ascites, enlarged tender liver, pallor, jaundice, Hb 8, TLC 3.3, PLT 90, ALT 200, bilirubin 55, urine hemosiderin and bilirubin +, US: enlarged liver, ascites, absent flow in hepatic veins >>> **PNH (Budd-Chiari syndrome)**.

### G6PD Deficiency (Glucose-6-phosphate dehydrogenase deficiency)

G6pd deficiency is **the commonest red cell enzyme defect**.

↓ G6PD → ↓ glutathione → increased red cell susceptibility to oxidative stress

It is more common in people from Mediterranean, Africa, Afro-Caribbean, Iraqi, Jew, South East Asian and Chinese.

It is inherited **as X-linked recessive** fashion, so **males** are mostly affected (No male to male transmission).

It predisposes to a haemolytic anaemia reaction with drugs or infection.

The haemolytic anaemia is non-immune so direct antiglobulin test (DAT) will be negative.

Many drugs can precipitate a crisis as well as infections and broad (fava) beans.

Treatment revolves around avoidance of all known precipitating factors, and blood product support should only be given in unstable, symptomatic patients.

Features:

- Neonatal jaundice.
- Intravascular haemolysis
- **RBCs Heinz bodies on blood film** (oxidised denatured haemoglobin).
- **Acute abdomen**

Diagnosis: **G6PD enzyme assay**

Drugs causing haemolysis (5): طفل انيميا الفول بلاش يروح افريقيا علشان الملاريا وعلاجها ☹

- 1) **Aspirin.**
- 2) **Anti-malarial: Primaquine, Quinine/quinidine, Chloroquine.**
- 3) **Sulpha-** group drugs: Sulphonamides, Sulfamethoxazole, Sulphasalazine, Sulfonyleureas.
- 4) **Ciprofloxacin.**
- 5) **Nitrofurantoin**

Safe drugs: ☺

- Penicillins
- Cephalosporins
- Macrolides
- Tetracyclines
- Trimethoprim

In "Co-trimoxazole": the sulfamethoxazole causes haemolysis in G6PD, not the trimethoprim.

**EX:** Male boy 16 years old with acute abdomen, jaundice, fever, anaemia with Hb 6, high LDH 1500 >>>? G6PD deficiency.

**EX:** A **62**-year-old Caribbean man with new onset type 2 DM presents to the ER. He has increasing lethargy and tiredness since starting a sulphonylurea a few days earlier.

On examination he has jaundiced sclerae, his BP is 135/72 mmHg, and pulse is 95. His mucous membranes look a little pale.

Lab: Hb=10, Bilirubin = 80 µmol/L (N <17), Heinz bodies in peripheral film.

The most likely diagnosis is **G6PD deficiency**.

**EX:** A **60**-year-old Chinese man has been started by his GP on quinine for leg cramps. He presents, a week later, with 5 days of darkened urine and 2 days of increasing breathlessness, back pain and fatigue.

Lab: Hb of **70** g/L (130-180) and raised reticulocyte count.

The best to explain this drug reaction >>> **G6PD**.

**EX:** Pt take Dapsone for malaria prophylaxis before trip to Kenya, the presented with confusion, tachypnea, desaturation, tachycardia, hypotension, anaemia HB 8, ↑RTX >>>> the diagnosis is that of **methaemoglobinaemia secondary to Dapsone** in a patient with underlying (**G6PD**) deficiency >>> TTT **Exchange blood transfusion**.

Methaemoglobinaemia in G6PD-deficient patients is best treated with **exchange transfusion**.

**Hereditary spherocytosis (HS)**

- The **most common hereditary haemolytic anaemia** in people of **northern European** descent.
- **Autosomal dominant** defect of red blood cell cytoskeleton (usually the spectrin component) causing spherocytes in blood film.
- The normal biconcave disc shape is replaced by a sphere-shaped RBC
- ↓ RBCs survival as destroyed by the spleen.
- Hereditary spherocytosis is usually an incidentally detected condition unless the person has active **haemolysis**, **gall stones** or uncomfortable **splenomegaly**. In this situation, which is not uncommon, the presentation is with gall stones.

**Presentation:**

- Failure to thrive
- Jaundice, gallstones
- Splenomegaly
- **Aplastic crisis** precipitated by **parvovirus** infection
- Degree of haemolysis variable
- ↓low MCV & MCH, ↑high MCHC (due to hyperdense cells), ↑LDH, ↑Unconjugated bilirubin, ↑RTX, ↓Haptoglobin.
- Direct Coombs' test (DCT) is negative. As it is not an immune haemolysis.

**Diagnosis:**

- **Osmotic fragility test:** (Rupture of Spherocytes in mildly hypotonic solution), but this has now been replaced by the **eosin-5-maleimide** binding to red cells and then being detected by flow cytometry.

The osmotic fragility test is unreliable and is no longer recommended in routine clinical practice. Osmotic gradient ektacytometry is used to differentiate hereditary spherocytosis from hereditary stomatocytosis, but is only available in specialised laboratories. If the diagnosis is equivocal, the cryohaemolysis test and EMA binding can be used. In atypical cases, gel electrophoresis analysis of erythrocyte membranes is the test of choice.

**Management:**

- 1) Folate replacement
- 2) **Splenectomy**: it should be performed after the age of 6 years and with appropriate counselling about the infection risk.

It is important to rule out stomatocytosis where splenectomy is contraindicated because of the thrombotic risk.

**Comparing G6PD deficiency to hereditary spherocytosis:**

	<b>G6PD deficiency</b>	<b>Hereditary spherocytosis</b>
<b>Gender</b>	Male (X-linked recessive)	Male + female (autosomal dominant)
<b>Ethnicity</b>	Mediterranean + African	Northern European
<b>Typical history</b>	<ul style="list-style-type: none"> <li>• Neonatal jaundice.</li> <li>• Infection/drugs precipitate haemolysis.</li> <li>• Gallstones.</li> </ul>	<ul style="list-style-type: none"> <li>• Neonatal jaundice.</li> <li>• Chronic symptoms although haemolytic crises may be precipitated by infection.</li> <li>• Gallstones.</li> <li>• Splenomegaly is common.</li> </ul>
<b>Blood film</b>	<u>Heinz bodies</u>	<u>Spherocytes</u> (round, lack of central pallor)
<b>Diagnostic test</b>	Measurement G6PD enzyme activity	Osmotic fragility test

**Ex:** The clue of hereditary spherocytosis >> by the normocytic anaemia, gallstones and family history.

**EX:** Pt with **hereditary spherocytosis + acute abdomen** >> think of: **Biliary colic** or **rupture spleen**.

**NB:** Red cell membrane defects are broadly classified into hereditary spherocytosis (HS), hereditary elliptocytosis (HE) and others.

**Horizontal** membrane protein defects (for example, spectrin ankyrin interaction defect) results in HE whereas vertical defects result in hereditary spherocytosis.

**Elliptocytosis** is usually caused by **spectrin** and spectrin-protein 4.1 defects.

**Heterozygotes** are **asymptomatic** but show elliptocytes on blood film; they do **not** have haemolysis and do **not** require any particular treatment.

### **Sickle cell disease (SCD)**

Sickle cell anaemia (SSA) is characterised by periods of good health with intervening crises.

It is inherited as **autosomal recessive**.

It is caused by mutation in **β globin chain of Hb**, causing hydrophilic amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the **6<sup>th</sup>** position.

The β globin gene is found on the short arm of **chromosome 11**.

The association of 2 wild type α globin subunits with 2 mutant β globin subunits → forms haemoglobin S (**Hb S**).

**HbS** has a life span of **only 30 days** compared to the normal 120 days.

**HbS** has the following properties:

- It contains **two α-like** globins and **two β-like** globins and **four haem** molecules.
- It is the result of a **point mutation** substituting glutamate for **valine** at position **6 in chromosome 11 for beta chain**.
- It is **less negatively** charged, due to the loss of glutamate for valine.
- The loss of the negative charge and the configuration of HbS makes it **less soluble** than HbA.
- It has **lower affinity for oxygen** than HbA (**right-shift** of the oxygen-dissociation curve), which increases the risk of **desaturation**, but improves the yield of oxygen to the tissues.
- It polymerises with adjacent HbS.

**Sickle cell disease** is **most common** in regions where **P.falciparum malaria** is endemic and in ethnic groups that have migrated from these areas.

The sickle cell gene is most prevalent in areas where **malaria** is also prevalent. This genetic abnormality is not caused by malaria, but the selective advantage of the



carrier state in malarial regions has allowed it to persist in the gene pool (positive selective evolutionary pressure).

Patients with **sickle cell trait** have just as **much risk** of contracting **P. falciparum malaria** compared with patients with HbAS or HbAA.

Patients with **HbSS** are at higher risk of **severe** malaria with complications and have a higher mortality rate.

However, the reduced red cell life cycle in HbAS reduces parasitaemia, which reduces the risk of severe disease and neurological complications (for example, seizures and coma).

Types:

- 1) Sickle cell anaemia is a specific form of sickle cell disease in which there is **homozygosity** for the mutation, it is also known as “Haemoglobin S”, “Hb SS”, “SS disease”.
- 2) **Heterozygous**: 1 sickle gene and 1 normal gene, it is known as “Hb AS” or “Sickle cell trait”.
- 3) **Other, rarer forms** of sickle cell disease in which there are compound heterozygous state in which the person has only one copy of the mutation that causes Hb S and one copy of another abnormal Hb allele. Examples:
  - “HbSC”: (sickle –haemoglobin C disease).
  - “HbS/β<sup>+</sup>”: (sickle-beta-plus-thalassemia).
  - “HbS/β<sup>0</sup>”: (sickle-beta-zero-thalassemia)

**Four** main types of crises are recognised:

- 1) Thrombotic, 'painful crises' (vaso-occlusive crises)
- 2) Sequestration (spleen, liver, kidney or lungs)
- 3) Aplastic (Parvovirus)
- 4) Haemolytic

**Thrombotic crises = Painful crises or Vaso-occlusive crises:**

- Precipitated by infection, dehydration, deoxygenation
- Infarcts occur in various organs including the bones (e.g. avascular necrosis of hip, hand-foot syndrome in children, lungs, spleen and brain).
- **Functional hyposplenism** in SCD also renders sufferers susceptible to infection with **encapsulated** bacteria (pneumococci, meningococci).
- Patients with sickle cell disease have a predisposition to develop osteomyelitis due to Salmonella species.

**Salmonella osteomyelitis** is seen in patients with sickle cell anaemia.

**Sequestration crises:**

- Sickling within organs such as the spleen, liver, kidney or lungs causes pooling of blood with worsening of the anaemia
- **Acute chest syndrome:** dyspnoea, chest pain, pulmonary infiltrates, low pO<sub>2</sub> - the most common cause of death in **adult**. (Hydroxyurea ↓ incidence of acute chest syndrome).
- The most common cause of death in **childhood** is: infarction (CVS) and infection (pneumococcal, chlamydia, mycoplasma).
- 5-10% of sickle cell patients will suffer a stroke, usually during childhood. The risk can be predicted by transcranial Doppler measurement of middle cerebral artery (MCA) flow rate, and prompt institution of a prophylactic transfusion program to reduce the HbS % can prevent further strokes. When **stroke** is occurred with lateralization >>> TTT: **Exchange transfusion programme** (**NOT** thrombolytic therapy, **NOT** Hydroxyurea, **NOT** BMT).

**EX:** Pt. with sickle cell anaemia presents with abdominal pain + **splenomegaly+ anaemia** >>> so, It is a **Sequestration crises**.

**Acute chest syndrome:**

It is defined as a '**new infiltrate**' consistent with consolidation at least segmental in size, **and one of:**

- **Chest pain**,
- **Fever**, a temperature > 38.5°C,
- **Shortness of breath** (tachypnoeic, wheezing, cough or low O<sub>2</sub> sat).

It is important to remember that not all of the above features will be present at the same time, CXR changes often lag behind, i.e. CXR may be normal initially, and subsequent imaging will reveal an infiltrate.

The syndrome can develop because of infection, infarction or a combination of the two.

Although lung new infiltrates in CXR are a characteristic feature of acute chest syndromes, it is important to remember that they can lag behind, and treatment should not be delayed in the absence of CXR changes if all other clinical signs suggest acute chest syndrome.

The key is to have a high index of suspicion and monitor vital signs particularly oxygen saturations regularly and anticipate development of possible acute chest syndrome. Early recognition and treatment is lifesaving.

Chest pain is often a feature of acute chest syndrome, either from the onset or presents later during the course of disease.

Shortness of breath is an important feature of acute chest syndrome and one of the main markers of deterioration indicating the need for possible exchange transfusion.

Fever, usually temperature of greater than 38.5°C is another recognised feature of acute chest syndrome. All patients with temperatures more than 38°C should have cultures sent.

Acute chest syndrome is a combination of signs and symptoms, not all of them need to be present for a diagnosis to be made.

**Hydroxyurea** reduces the incidence of acute chest syndrome and the need for blood transfusion in people with SCD over a mean of 21 months.

#### **Aplastic crises:**

- Caused by infection with **parvovirus B19**.
- The virus infects red cell progenitors in bone marrow, resulting in cessation of erythropoiesis and a **very rapid drop in haemoglobin**.
- **Sudden fall** in Hb **without an appropriate** ↑reticulocytosis.
- The condition is **self-limited**, with bone marrow recovery occurring in 7-10 days, **followed by brisk reticulocytosis**.

#### **Haemolytic crises:**

- Rare
- Fall in haemoglobin due an increased rate of haemolysis

The mechanism of action of **hydroxycarbamide (Hydroxyurea)** in the setting of its use in **sickle** cell disease >>> **stimulating** the **production** of **fetal haemoglobin (Hb F)** which protects against sickling.

**Hydroxyurea is HbF switching therapy.**

It is **not** used in the **acute** setting.

A pregnant woman attends for her booking antenatal appointment. How will screening for sickle cell disease be undertaken?

**She will first be screened for sickle cell carrier status. If that test is positive, her partner will be screened, and only if both are positive and confirmed by genetic testing, she will be offered chorionic villus sampling (CVS) or amniocentesis.**

In low prevalence trusts laboratory screening is only carried out if the baby is identified as being at risk of a haemoglobinopathy based on the family origin questionnaire and a routine full blood count from the mother.

In **high prevalence trusts** all women undergo the **initial** laboratory **screening** to identify **if the mother carries** the sickle cell gene, regardless of family origin. However, the family origin questionnaire still needs to be completed to facilitate diagnosis of the type of haemoglobinopathy.

The **father** is tested for carrier status **only if** the mother is found to be a carrier.

If **both** are found to be carriers this is **confirmed by genetic testing** before offering chorionic villus sampling (**CVS**) (8-10 weeks) or **amniocentesis** (14-16 weeks).

The **anaemia** associated with sickle cell disease is usually **only symptomatic below 70 g/L**, as oxygen is released more readily from erythrocytes.

There is a tendency to **iron overload** in sickle cell disease and **therefore oral iron therapy is not usually indicated**.

A **urine concentrating defect** is quite common in sickle cell anemia.

The **spleen is decreased in size** after 6 months of age, due to repeated episodes of venoocclusion and infarction, and patients often have **functional hyposplenism (auto-splenectomy)** and so they are recommended to take **daily penicillin**.

SCD patients are at much higher risk from gall stones disease due to chronic hyperbilirubinaemia.

Intra-articular steroids have been associated with a sickle cell crisis, the mechanism of which is not fully understood, but they should be avoided. ☹

All adults who have **hyposplenism**, including patients with **SCD**, need:

- 1) Yearly **influenza** vaccine.
- 2) **Pneumococcal** C vaccine, (adults and children over 2 years) repeated every five years.

- 3) **Haemophilus influenzae** type b; if not already given as part of childhood immunisation.
- 4) **Conjugated meningococcal C vaccine**; if not already given as part of childhood immunisation.
- 5) **Meningococcal ACWY vaccine**; if travelling to areas with high risk of meningitis.

Although patients with sickle cell disease do need the **yearly influenza** vaccination, they also need **five yearly Pneumovax**.

### **Sideroblastic anaemia**

Sideroblastic anaemia is a condition where red cells fail to completely form haem, whose biosynthesis takes place partly in the mitochondrion.

This leads to deposits of iron in the mitochondria that form a ring around the nucleus called a ring sideroblast.

It may be congenital or acquired:

**Congenital cause**: delta-aminolevulinate synthase-2 deficiency.

**Acquired causes**:

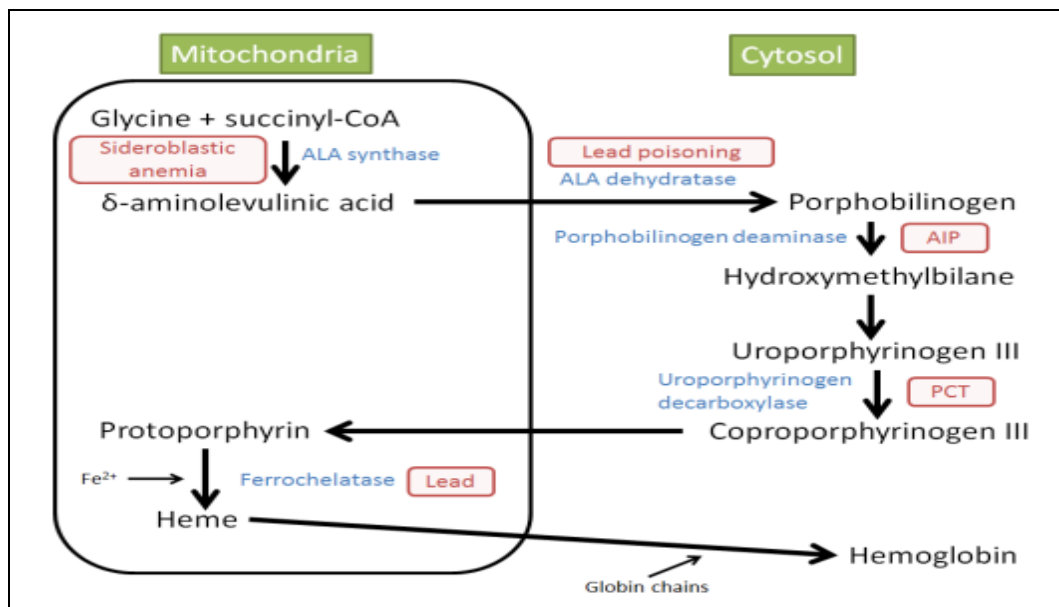
- 1) Lead
- 2) Alcohol
- 3) Myelodysplasia
- 4) Drugs: Anti-TB medications, chloramphenicol.

**Investigations**:

- **Hypochromic microcytic anaemia** (more so in congenital)
- **Bone marrow**: sideroblasts and increased iron stores in BM.

**Management**:

- Supportive
- Treat any underlying cause
- **Pyridoxine** may help



### Haemochromatosis: investigation

Haemochromatosis is an **autosomal recessive** disorder of iron absorption and metabolism resulting in iron accumulation.

It is caused by inheritance of mutations in the **HFE gene** on both copies of **chromosome 6**. (There are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene).

Haemochromatosis is **the most prevalent genetic condition in Caucasian** population, with a carrier rate of 1 in 10 and is present in about 1 in 200-400 people.

Cystic fibrosis (CF) has a carrier rate of 1 in 25 and is present in about 1 in 2500 births. So **CF** is often considered as **the most common lethal inherited condition in Caucasians**.

**So haemochromatosis is more common than cystic fibrosis.**

There is continued debate about the best investigation to **screening** for haemochromatosis. The 2000 BCSH guidelines suggest:

- 1) **General population: Transferrin saturation** is considered the most useful marker. **Ferritin** should also be measured but is not usually abnormal in the early stages of iron accumulation.
- 2) **Testing family members: genetic testing for HFE mutation.**
- 3) These guidelines may change as HFE gene analysis become less expensive.

**Haemochromatosis screening:**

- General population: Transferrin % > Ferritin.
- Family members: HFE genetic testing.

**Presenting features:**

- 1) Often asymptomatic in early disease and initial symptoms often non-specific e.g. lethargy, **erectile dysfunction**, **arthralgia/arthritis often of the hands** esp. the 2<sup>nd</sup> and 3<sup>rd</sup> metacarpo-phalangeal joints.
- 2) **Bronze skin pigmentation** (Skin pigmentation rather than a rash).
- 3) **DM**.
- 4) **Liver**: stigmata of chronic liver disease, hepatomegaly, cirrhosis, hepatocellular deposition.
- 5) **Cardiac** failure (secondary to **DCM**).
- 6) Hypogonadism (secondary to cirrhosis and pituitary dysfunction-**Hypogonadotrophic hypogonadism**).

Reversible complications	Irreversible complications
<ul style="list-style-type: none"> <li>• Cardiomyopathy</li> <li>• Skin pigmentation</li> </ul>	<ul style="list-style-type: none"> <li>• Arthropathy</li> <li>• DM</li> <li>• Liver cirrhosis</li> <li>• Hypogonadotrophic hypogonadism</li> </ul>

**Both** males and females are affected equally, but females are often 'protected' from the clinical features by menstrual blood loss.

**Early** diagnosis and treatment is critical in haemochromatosis as survival and morbidity are improved if phlebotomy is initiated prior to the development of cirrhosis.

**Transferrin saturation** is suggested as the initial screening test: a level of more than 45% warrants further investigation (less than 45% usually excludes the diagnosis). Genetic screening is then performed. If the usual C282Y HFE mutation is found this makes the diagnosis.

If the C282Y HFE mutation is not present other genotypes should be looked for and if present a liver biopsy is indicated.

**Ferritin** is measured to help guide further investigation and treatment: **if more than 1000 >>> a liver biopsy** should be performed and treatment initiated.

If the ferritin is within normal range and the liver function tests are normal patients can be followed closely.

**Diagnostic tests:**

- Molecular genetic testing for the C282Y and H63D mutations
- Liver biopsy: Perl's stain

**Typical iron study profile in patient with haemochromatosis:**

- 5) ↑ Iron.
- 6) Low TIBC.
- 7) ↑ Ferritin (e.g. > 500 ug/l) and
- 8) ↑ Transferrin saturation > **55%** in men or > **50%** in women.

**Treatment:**

The goal of therapy is to remove excess body iron stores which is commonly done via **phlebotomy**. Initially this is **weekly** or **twice weekly** (if tolerated) venesections of 500 cm<sup>3</sup> until the serum ferritin is less than 50 ng/mL. Transferrin saturation should also be reduced to less than 50% if possible.

Monitoring adequacy of venesection: BSCH recommends:

**Transferrin saturation** should be kept below **50%** and the serum **ferritin** concentration below **50 ug/l**.

After these goals are reached maintenance therapy is typically required three to four times per year. When iron overload and anaemia are present concomitantly **chelation with desferoxamine** may be required.

Patients should be told to avoid vitamin C supplementation as this can enhance iron toxicity.

End stage liver disease, portal hypertension and hepatocellular carcinoma (which is increased up to 200-fold) may necessitate liver transplantation.

**N.B:** Joint x-rays characteristically show **chondrocalcinosis**.

**EX:** A 36-year-old male with Type 1 DM of 3 years duration presented with decreased libido and erectile dysfunction since diagnosis. No abnormalities were noted on genital examination. Lab: with **low testosterone** and **low FSH** >>> **Haemochromatosis** >>> Check serum **ferritin**.



## Polycythaemia

Polycythaemia may be relative, primary (polycythaemia rubra Vera) or secondary.

Relative causes ( <b>Pseudo</b> -polycythaemia)	<b>Primary</b>	<b>Secondary</b> causes (due to ↑ <b>EPO</b> )
<ul style="list-style-type: none"> <li>• <u>Dehydration</u></li> <li>• Stress: Gaisbock syndrome</li> </ul>	PRV	<ol style="list-style-type: none"> <li>1) <u>COPD</u></li> <li>2) <u>Obstructive sleep apnoea</u></li> <li>3) <u>High attitude.</u></li> <li>4) <u>Excessive erythropoietin (Erythropoietin-secreting tumours):</u> <ul style="list-style-type: none"> <li>○ Cerebellar haemangioma,</li> <li>○ <u>Hypernephroma</u>,</li> <li>○ Hepatoma (<u>HCC</u>),</li> <li>○ <u>Uterine fibroids</u> (as it may cause menorrhagia which in turn leads to blood loss - polycythaemia is rarely a clinical problem).</li> </ul> </li> </ol>

To differentiate between true (primary or secondary) polycythaemia and relative polycythaemia **red cell mass** estimation with **51 Cr radiolabelled Chromium** is sometimes used, it isn't so easy to obtain.

In true polycythaemia: ↑ **Red cell mass** (N=1312-2187 ml), ↑ **Haematocrit**, **low-normal plasma volume** (N= 2362-3938 ml).

In **true** polycythaemia **the total red cell mass** in males > 35 ml/kg and in women > 32 ml/kg.

In **secondary** polycythaemia as a consequence of respiratory diseases or renal cell carcinoma is characterised by **high levels of circulating plasma EPO driving erythropoiesis** (Normal serum EPO is up to 20 mU/ml).

The discovery of the **JAK2 mutation** has made red cell mass a second-line investigation for patients with suspected JAK2-negative PRV.

JAK2 is a crucial tyrosine kinase which transmits the EPO signal to increase red cells production.

The **most specific** with respect to **confirming** the diagnosis of primary polycythaemia (PRV) **versus** a diagnosis of secondary polycythaemia is >>> **JAK2 mutation screening**.

Polycythaemia rubra Vera (PRV) >>> **JAK2 mutation**

**Von Hippel Lindau syndrome:** is **autosomal dominant** condition, it is a **secondary** polycythaemia, it can lead to **retinal** and **CNS tumours** as well as **pheochromocytoma**. **Death** is often due to **renal cell carcinoma**. A proportion of **cerebellar haemangiomas** secrete erythropoietin-like substance, leading to a **secondary** polycythaemia.

**EX:** Female 55 years old, dizziness, Hb 22, Nystagmus, ataxia, broad-based gait, dilated retinal veins on fundoscopy >>> **Von Hippel Lindau syndrome**.

### **Polycythaemia rubra Vera (PRV)**

PRV is a **myeloproliferative disorder** caused by clonal proliferation of a marrow stem cells (erythroid, myeloid and megakaryocytic elements) leading to a **↑ RBCs**, **often accompanied by overproduction of neutrophils and platelets**.

It has peak incidence in the **sixth decade**, with typical features including hyperviscosity, pruritus and splenomegaly.

It has an incidence of 5-17/million population/year.

It has recently been established that a **mutation in JAK2** is present in approximately **95%** of patients with **PRV** and this has resulted in significant changes to the diagnostic criteria.

Eventual transformation of primary polycythaemia (PRV) may occur to AML, CML and CLL.

Features:

- 1) **Hyperviscosity:** (headache, tinnitus, visual disturbance, arterial and venous **thrombosis**, stroke like limb weakness, TIA, Budd-Chiari syndrome, portal vein thrombosis, angina, intermittent claudication)
- 2) **Pruritus**, typically after a hot bath
- 3) **Splenomegaly**
- 4) Haemorrhage (secondary to abnormal platelet function NOT NUMBER)
- 5) Plethoric appearance
- 6) Hypertension in a third of patients
- 7) **Low ESR**

- 8) **Raised leukocyte ALP.**
- 9) **Mild prolonged PT & PTT:** this is related to the ratio of plasma and citrate. In the blue tubes that are used for coagulation tests the ratio is normally 1 citrate to 9 of whole blood. If there is less plasma due to the polycythaemia there will be excess citrate and this will prolong coagulation tests such as the APTT and prothrombin time.
- 10) Others: hyperuricaemia, peptic ulceration.

Following history and examination, the British Committee for Standards in Haematology (BCSH) recommend the following tests are performed:

- 1) CBC/film (raised haematocrit; neutrophils, basophils, platelets raised in half of patients)
- 2) JAK2 mutation
- 3) Serum ferritin
- 4) Renal and liver function tests

If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:

- Red cell mass
- Arterial oxygen saturation
- Abdominal ultrasound
- ↓ Serum erythropoietin level
- Bone marrow aspirate and trephine
- Cytogenetic analysis
- Erythroid burst-forming unit (BFU-E) culture

**The diagnosis of PRV is based on the revised WHO criteria.**

Diagnosis requires two major criteria and one minor criterion, or the first major criterion and two minor criteria.

**Major criteria:**

- 1) **Haemoglobin** of more than 185 g/L in men, 165 g/L in women, or **elevated red cell mass** > 25% above mean normal predicted.
- 2) Presence of **JAK 2 mutations**, commonly 617V F

**Minor criteria:**

- 1) **Bone marrow biopsy** showing hypercellularity with prominent erythroid, granulocytic and megakaryocytic proliferation
- 2) **Serum EPO below** normal range
- 3) Endogenous erythroid colony formation in vitro.

Oxygen saturations, splenic size, platelet count and white cell count no longer feature in the diagnostic criteria.

**The diagnostic criteria for PRV** have recently been updated by the BCSH. This replaces the previous PRV Study Group criteria.

**JAK2-positive PRV:** diagnosis requires both criteria to be present:

A1	High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted)
A2	Mutation in JAK2

**JAK2-negative PRV:** diagnosis requires A1 + A2 + A3 + either another A or two B criteria:

A1	Raised red cell mass (>25% above predicted) OR haematocrit >0.60 in men, >0.56 in women
A2	Absence of mutation in JAK2
A3	No cause of secondary erythrocytosis
A4	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality (excluding BCR-ABL) in the haematopoietic cells
B1	Thrombocytosis (platelet count >450 * 10 <sup>9</sup> /l)
B2	Neutrophil leucocytosis (neutrophil count > 10 * 10 <sup>9</sup> /l in non-smokers; > 12.5*10 <sup>9</sup> /l in smokers)
B3	Radiological evidence of splenomegaly
B4	Endogenous erythroid colonies or low serum erythropoietin

**Management:**

- 1) **Venesection** - first line treatment, it will lessen the rates of thrombotic complications but there is no evidence that venesection improves long term survival rates.
- 2) Aspirin
- 3) Hydroxyurea -slight increased risk of secondary leukaemia
- 4) Phosphorus-32 therapy

**Prognosis:**

- 1) **Thrombotic events** are a significant cause of morbidity and mortality.
- 2) 5-15% of patients progress to **myelofibrosis**.
- 3) 5-15% of patients progress to **acute myeloid leukaemia (AML)** (risk increased with chemotherapy treatment).

The most common types of transformations seen in patients with polycythaemia rubra Vera >> **myelofibrosis** and **AML**.

**Methaemoglobinaemia**

It describe Hb which has been **oxidized from Fe<sup>++</sup> (ferrous) to Fe<sup>+++</sup> (Ferric)**.  
**(Fe<sup>++</sup> >> Oxidation >> Fe<sup>+++</sup>)**

This is **normally** regulated by **NADH methaemoglobin reductase**, which transfers electrons from NADH to methaemoglobin resulting in the reduction of methaemoglobin to haemoglobin.

There is **tissue hypoxia** as Fe<sup>+++</sup> cannot bind oxygen, and hence the oxygen-Hb dissociation (oxidation-dissociation) curve is **shift to left**.

**Congenital causes:**

- Hb chain variants: HbM, HbH
- NADH methaemoglobin reductase deficiency.

**Acquired cause:**

- Drugs:
  - Na Nitroprusside,
  - Nitrates,
  - Drinking water contaminated with nitrates,
  - Drinking a flask of amyl nitrate (in nightclub),
  - Primaquine (malaria prophylaxis ttt),
  - Sulphonamides (Trimethoprim),

- Dapsone.
- Chemicals: Aniline dye.

**Features:**

- 1) **Chocolate central cyanosis**, the blood also appears chocolate brown when compared with normal blood.
- 2) **Dyspnoea**.
- 3) ↓ **Oxygen saturation** with **NORMAL PO<sub>2</sub>**
- 4) Despite increase oxygen delivery even the non-rebreather mask, the O<sub>2</sub> saturation remain low.
- 5) Severe: **acidosis, anxiety**, arrhythmia, seizures, coma.

**Severity** of symptoms usually correlates with **measured methaemoglobin (MetHb) levels**:

- Mild methaemoglobinaemia (< 15-20%) usually resolve spontaneously and requires no intervention.
- The discolouration of blood and appearance of cyanosis manifests when the MetHb levels reach **15-20%**.
- Levels between 20-45% are associated with dyspnoea, lethargy, dizziness and headaches.
- MetHb levels above 45% are usually associated with impaired consciousness
- Levels above 55% can cause seizures, coma and cardiac arrhythmias.
- The lethal concentration for adults is considered to be more than 70%.

**Management:**

- **Methylene blue 1% IVI** (1-2 mg/kg IVI over several minutes): in acquired causes. It is the **initial** treatment of choice especially when methaemoglobin level is >20%, it should be administered with care as at high dose > 7 mg/kg it becomes an oxidant itself.
- **Ascorbic acid**: in NADH methaemoglobin reductase deficiency. It is a second line therapy although some debate exists as to its efficacy.
- **Exchange transfusion**.
- **Hyperbaric oxygen therapy**

**EX:** Pt take Dapsone for malaria prophylaxis before trip to Kenya, the presented with confusion, tachypnea, desaturation, tachycardia, hypotension, anaemia HB 8, ↑RTX >>>> the diagnosis is that of **methaemoglobinaemia secondary to Dapsone** in a patient with underlying (**G6PD**) deficiency >>> TTT **Exchange blood transfusion**.

Methaemoglobinaemia in G6PD-deficient patients is best treated with **exchange transfusion**.

NB: Methylene blue is contraindicated in patients with G6PD deficiency as it can lead to severe haemolysis.

### **Fanconi's Anaemia:**

- Autosomal recessive
- Aplastic anaemia
- ↑ risk of AML
- Neurological manifestation
- Skeletal abnormalities
- Skin pigmentation (café; au lait spots)

### **Myeloproliferative disorders**

- 1) Polycythaemia rubra Vera (PRV).
- 2) Essential Thrombocythaemia (ET).
- 3) AML and CML.
- 4) Myelofibrosis.

For:

- **Bone marrow cytogenetic.**
- Peripheral blood **molecular analysis** (PCR): BCR-ABL translocation (t[9:22]) in CML.
- Peripheral blood **Immunophenotyping.**

### **Acute myeloid leukaemia (AML)**

Acute myeloid leukaemia is **the more common form of acute leukaemia in adults.**

It may occur as a **primary** disease or **following a secondary transformation** of a myeloproliferative disorder e.g. CML, myelofibrosis.

Presentation:

- Vague and non-specific (flu-like symptoms)
- Due to **pancytopenia** (Infection, anaemia, bleeding)
- Splenomegaly may occur but typically mild and asymptomatic.
- LN swelling is rare.
- High TLC leads to leucostasis and hyperviscosity >> drowsiness and retinal vein dilatation.
- Blood film reveals white cells predominantly myeloblasts and promyelocytes.

Poor prognostic features:

- 1) **> 60 years**

- 2) **> 20% blasts** after first course of chemo
- 3) **Cytogenetic: deletions of chromosome 5 (5q-) or 7 (7q-)**

**AML >>> Cytogenetics Karyotype of BM** it is of **most prognostic value**.

Classification - French-American-British (FAB):

- MO - undifferentiated
- M1 - without maturation
- M2 - with granulocytic maturation
- **M3 - acute promyelocytic (APML)**
- M4 - granulocytic and monocytic maturation
- **M5 - monocytic**
- M6 - erythroleukaemia
- M7 - megakaryoblastic

ALL cells characteristically stain positive for **PAS** (Periodic acid-Schiff) and **NSE** (Non-specific Esterase).

AML cells characteristically stain positive for **Sudan Black** and **myeloperoxidase**, but M4 and M5 cells stain positive for NSE, while M6 cells stain positive for PAS.

**Acute promyelocytic leukaemia (APML) M3:**

- **Good prognosis.**
- It is characterised by a chromosomal translocation involving the **retinoic acid receptor-alpha** gene on chromosome 17 (RARA).
- In 95% of cases, retinoic acid receptor-alpha (**RARA**) gene on chromosome **17** is involved in a reciprocal translocation with the promyelocytic leukaemia gene (**PML**) on chromosome **15**.
- Associated with t (15; 17).
- The mechanism underlying leukaemogenesis is **aberrant fusion of 2 genes** PML and RARA.
- Presents **younger** than other types of AML (average = **25** years old).
- **Auer rods** (seen with myeloperoxidase stain).
- **DIC** (FDPs & D-Dimer) or **thrombocytopenia often at presentation.**



**TTT of AML:** Combination chemotherapy including arabinosylcystosine after apheresis.

**TTT of APML:** (differs from that of all other AML forms): **All-trans-retinoic acid (ATRA)**; a derivative of **vitamin A**.

**AML** is differentiated from **ALL** by the presence of **Auer rods** which are **eosinophilic needle-like cytoplasmic inclusions found in blast cells** and which are **pathognomonic of AML**.

**NB:** In AML >> **chromosomal abnormalities** detected by **cytogenetics** are the single most important **prognostic** factor.

**EX:** Male 55 yrs. Hb=8.6 g/dl, PLT=  $42 \times 10^9/l$ , TLC=  $36.4 \times 10^9/l$ , Blood film shows 30% myeloid blasts with Auer rods >>> so AML, good prognosis: t(15;17) i.e M3.

**EX:** A patient with AML develops jaundice and spiking pyrexia 3 weeks into induction chemotherapy. The patient remained pyrexial after 7 days of IV antibiotics.

What is the likely diagnosis >>> **CMV (Cytomegalovirus)**

The most likely cause for the **persisting pyrexia** plus **hepatitis** in this **immunocompromised** patient treated with **appropriate antibiotics** would be a **CMV** infection.

AML (**monocytic**) **M5: high count of circulating blasts** >>> may lead to symptoms of cellular hyperviscosity (headache, confusion, fits, coma) and tissue deposits of leukaemia cells (gums hypertrophy) with cells stain positive with Sudan Black and myeloperoxidase plus **NES**.

**Chronic myeloid leukaemia (CML)**

The **Philadelphia chromosome** is present in more than **95%** of patients with chronic myeloid leukaemia (CML).

It is due to a translocation between the long arm of chromosome 9 and 22 - **t(9:22)(q34; q11)**.

This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22.

The resulting **BCR-ABL gene codes for a fusion protein** which has **tyrosine kinase activity in excess of normal**.

Presentation:

- Middle-age (40-50 years).
- Anaemia, weight loss, abdomen discomfort.
- **Marked splenomegaly**.
- Myeloid cells spectrum are seen in peripheral blood.
- Decreased leukocyte alkaline phosphatase.
- May undergo blast transformation (AML in 80%, ALL in 20%).

Management:

- 1) **Imatinib mesylate (Glivec ®)** 400 mg daily: it is now considered **first-line treatment**: (It is **Tyrosine kinase Inhibitor** associated with the BCR-ABL fusion defect and it has very high response rate in chronic phase CML). So it is **Signal transduction inhibitor**. (S.E: **Diarrhea**, oedema, nausea, rash, CHF).
- 2) **Nilotinib** in patients who are Philadelphia chromosome positive and who are intolerant of imatinib.
- 3) Hydroxyurea.
- 4) Interferon-alpha.
- 5) Allogenic bone marrow transplant (the optimum ttt).

**Philadelphia chromosome:**

- **Good prognosis in CML,**
- **Poor prognosis in AML and ALL**

### **Leukaemoid reaction**

The Leukaemoid reaction describes the presence of immature cells such as myeloblasts, promyelocytes and nucleated red cells in the peripheral blood.

This may be due to infiltration of the bone marrow causing the immature cells to be 'pushed out' or sudden demand for new cells.

Causes:

- Severe infection
- Severe haemolysis
- Massive haemorrhage
- Metastatic cancer with bone marrow infiltration

A relatively common clinical problem is differentiating chronic myeloid leukaemia from a leukaemoid reaction. The following differences may help:

Leukaemoid reaction:

- 1) **↑ Leucocyte ALP score.**
- 2) **'Left shift'** of neutrophils i.e. three or less segments of the nucleus.
- 3) **Toxic granulation (Dohle bodies)** in the white cells.

Chronic myeloid leukaemia (CML):

- **low** leucocyte alkaline phosphatase score

### **Leukocyte alkaline phosphatase (LAP) score**

The LAP score aids in the differential diagnosis of CML versus leukaemoid reaction.

It also aids in the evaluation of:

- Polycythaemia vera
- Myelofibrosis with myeloid metaplasia, and
- Paroxysmal nocturnal haemoglobinuria.

High scores have been seen in:

- **Leukaemoid reactions**
- **Polycythaemia vera**

- **Myelofibrosis**
- Aplastic anaemia
- Downs syndrome
- Hairy cell leukaemia
- Neutrophilia either physiological or secondary to infection.
- Hodgkin disease.

**Low** scores have been associated with:

- 1) CML
- 2) Paroxysmal nocturnal haemoglobinuria (PNH)
- 3) Thrombocytopenic purpura (TTP), and
- 4) Hereditary hypophosphatasia.

#### Leucocyte alkaline phosphatase

Raised in	Low in
<ol style="list-style-type: none"> <li>1) <b>Infections</b></li> <li>2) <b>Leukaemoid reactions</b></li> <li>3) <b>Polycythaemia rubra vera</b></li> <li>4) <b>Myelofibrosis</b></li> <li>5) Steroids, Cushing's syndrome</li> <li>6) Pregnancy, OCP</li> </ol>	<ol style="list-style-type: none"> <li>1) <b>CML</b></li> <li>2) <b>PNH</b></li> <li>3) TTP</li> <li>4) Pernicious anaemia</li> </ol>

#### Acute lymphoblastic leukaemia (ALL): prognostic features

It causes damage and death by crowding out normal cells in the bone marrow and by metastasizing.

ALL is most common in childhood with a peak incidence at 2-5 years of age, and another peak in old age.

The overall cure rate in children is about 80% and about 45-60% of adults have long term disease-free interval.

Acute → relatively short course of the disease, being fatal in as little as a few weeks if untreated.

Terminal Deoxynucleotide Transferase (**TDT**) is present in 95% of ALL.

**Presentation:**

- Not specific
- Variable symptoms and signs
- Related to Bone marrow infiltration and/or organ infiltration
- The most common translocation is t(12:21) → good prognosis
- Others like Philadelphia chromosome t(9:22) & t(4:11) → bad prognosis.
- Dyspnoea due to lung infiltration
- Hepatosplenomegaly and lymphadenopathy

**Investigations:**

- Leucocytosis
- Blast cells are seen on blood smear in 90% of cases
- Bone marrow biopsy is conclusive proof of ALL
- LP to detect CNS involvement
- CXR to look for mediastinal mass
- U&E to look for tumour lysis syndrome
- Immunophenotyping to establish the blast cells origin is B or T lymphocytes.
- DNA testing (cytogenetics) as different mutations reflect prognosis

**Good prognostic factors:**

- 1) Common **ALL**
- 2) Pre-B phenotype
- 3) Low initial WBC
- 4) (FAB) L1 type
- 5) del(9p)

**Poor prognostic factors:**

- 1) FAB L3 type
- 2) T or B cell surface markers
- 3) Philadelphia translocation, t(9:22)
- 4) Age < 2 years or > 10 years
- 5) Male sex
- 6) CNS involvement
- 7) High initial WBC (e.g.  $\geq 100 \times 10^9/l$ )
- 8) Non-Caucasian

**N.B:** Before ALL ttt with chemotherapy, if blast cells count is very high ( $> 100 \times 10^9/l$ ) >> the patient needs **Leukapheresis** to prevent sludge in of capillary beds, this can be life-saving.

### Chronic lymphocytic leukaemia (CLL)

CLL is caused by a **monoclonal proliferation** of well-differentiated **lymphocytes** which are almost always **B-cells** (99%).

**CLL** is the **most common adult leukaemia** in western world.

#### Features:

- **Often none**
- It can be discovered incidentally.
- Constitutional: anorexia, weight loss, fever, chest infection
- Bleeding, infections
- Lymphadenopathy more marked than CML
- Hepatosplenomegaly

#### Complications:

- **Pan-Hypogammaglobulinaemia** leading to **recurrent infections** >> most common cause of death.
- **Warm AIHA** autoimmune haemolytic anaemia in **10-15%** of patients.
- Transformation to high-grade lymphoma (Richter's transformation).

#### Investigations

- 1) **CBC: High TLC with lymphocytosis and anaemia.**
- 2) Blood film: **smudge cells**; which are artefacts due to damaged lymphocytes during the slide preparation.
- 3) **Immunophenotyping (flow cytometry):** It is investigation of choice. It will demonstrate the cells to be B-cells (**CD 19** positive). **CD 5** and **CD23** are also characteristically positive.

**Anaemia in CLL:** may be secondary to **bone marrow involvement**, **splenic sequestration of RBCs** or **AIHA** associated with a +ve Coomb's test, spherocytosis,  $\uparrow$ MCV,  $\uparrow$  RTX.

According to Guidelines on the diagnosis and management of CLL, a definitive diagnosis of CLL is based on the combination of a **lymphocytosis** and **characteristic lymphocyte morphology** and **peripheral blood immunophenotype (flow cytometry)**.

A bone marrow (BM) is invasive and is sometimes not involved in low grade lymphoproliferative disorders and similarly there may be no cytogenetic abnormality. **(NO need for BM in CLL)** الراجل عجوز مش ناقص عينة نخاع

**CLL >>> Immunophenotyping (flow cytometry):** is investigation of choice.

EX: Old pt. with Hb 8, NN anemia, **TLC 25,000**, **↑ lymphocytes**, PLt 100 >>>? **CLL**

He is never going to be cured from this condition, and therefore **it would not be necessary to delay/cancel elective surgery for him**. He may be slightly more at risk of infection, due to immune dysfunction that accompanies these conditions, and the surgeons should be aware of this.

### **Management:**

It is a low grade condition, and does not require immediate treatment; patients undergo a period of **long observation** before any treatment is indicated.

There is no cure in this age group for CLL, therefore no benefit to early treatment.

Indications for treatment:

- 1) **Progressive marrow failure compromise:** the development or worsening of anaemia, neutropenia and/or thrombocytopenia.
- 2) **Progressive lymphocytosis:** > 50% rate of increase over 2 months or lymphocyte doubling time < 6 months.
- 3) Massive (>10 cm) or progressive **lymphadenopathy**.
- 4) Massive (>6 cm) or progressive **splenomegaly**.
- 5) **Systemic B symptoms:** weight loss > 10% in previous 6 months, fever >38°C for > 2 weeks, extreme fatigue, night sweats.
- 6) **Autoimmune** complications e.g. autoimmune haemolysis (spherocytosis, ↑bilirubin, ↑LDH and positive direct Coombs' test) or **ITP**.

Management:

- Patients who have no indications for treatment are **monitored** with regular CBC.

- **(FCR)** Fludarabine, Cyclophosphamide and Rituximab has now emerged as the initial treatment of choice for the majority of patients.
- **IVIG** to produce a rapid rise in the platelet, it usually has effect in about 48 hours.

**NB:** Patients on **Fludarabine (CLL)** are at increased risk of infection with **pneumocystis carinii pneumonia (PCP)**; for this reason they are recommended to take prior to treatment a **prophylaxis** with either **Co-trimoxazole** or **monthly nebulised pentamidine**.

### Chronic lymphocytic leukaemia: prognostic factors:

Poor prognostic factors (median survival 3-5 years):

- 1) Male sex
- 2) Age > 70 years
- 3) Lymphocyte count > 50
- 4) Lymphocyte doubling time < 12 months
- 5) Prolymphocytes comprising more than 10% of blood lymphocytes
- 6) Raised LDH
- 7) CD38 expression positive

Chromosomal changes:

- Deletion of the long arm of chromosome 13 (**del 13q**) is the most common abnormality, being seen in around **50%** of patients. It is associated with a **good** prognosis.
- Deletions of part of the short arm of chromosome 17 (del 17p) are seen in around 5-10% of patients and are associated with a poor prognosis.

**NB:** An **observation policy** is usual during the **early** stages of the disease. **Recurrent infections** are recognised in CLL due to **hypogammaglobulinaemia** and immune paresis; but are not an indication for disease control.

Pt with CLL is likely to benefit from regular infusions of **IVIG** to prevent infections.



### Hairy cell leukaemia

Hairy cell leukaemia is a rare malignant proliferation disorder of **B** cells (it is B lymphocytes disorder).

It is usually classified as a subtype of CML.

Hairy cells are abnormal WBCs with characteristic hair like projections (microvilli) of cytoplasm when seen by L/M or E/M.

Infiltration of the bone marrow leads to pancytopenia and the patient has hepatosplenomegaly.

It is more common in males (4:1).

Features:

- **Pancytopenia** (Monocytopenia is classical)
- **Large Splenomegaly**
- **Skin vasculitis** in 1/3 patients (cellulitis).
- Bone marrow aspirate: '**Dry tap**' despite bone marrow hypercellularity (as in myelofibrosis)
- Bone marrow biopsy → shows “**fried egg appearance**”
- The abnormal cells have Tartrate Resistant Acid Phosphatase (**TRAP**) stain **positive**
- Lymphadenopathy is very uncommon

Management:

- 1) It **responds dramatically** to the **purine analogue chemotherapy**, is first-line: cladribine & pentostatin, with resulting survival rates at 5 years of 95-98%.
- 2) Immunotherapy is second-line: rituximab, **interferon-alpha**
- 3) Splenectomy sometimes required.

**Hairy cell leukaemia >>> Interferon-alpha** : 2 million U/m<sup>2</sup> SC 3 times a week for 12-18 months can be used to salvage relapsed or refractory hairy cell leukemia.

**EX:** Pt with antibiotic resistant **leg cellulitis** and **pancytopenia** >>> Hairy cell leukaemia >>> for bone marrow aspirate (Dry tap) & biopsy (fried egg appearance).

**EX:** Old male 70 years old, **recurrent chest infection**, **large splenomegaly**, Hb 8, TLC 24, PLT 25, **absent monocytes**, blood film shows villous **projections** of atypical monocytes >>> **Hairy cell leukaemia**.

### Leukoerythroplastic Anaemia

It is left shifted granulocytic series and nucleated RBCs with pancytopenia.

It is also defined when there are **immature cells** e.g. **myelocytes** and **nucleated RBCs** seen on the peripheral blood film.

Association:

- 1) ↑Bone marrow turnover e.g. in severe haemolytic anaemia (↑RTX).
- 2) Myelofibrosis and CML (↑TLC, ↑PLT, Splenomegaly).
- 3) Bone marrow invasion.
- 4) Myeloma
- 5) PRV
- 6) Osteopetrosis
- 7) T.B infiltration of bone marrow.
- 8) Sarcoidosis

### Hodgkin's lymphoma: histological classification and prognosis

Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the malignant **Reed-Sternberg cell (RSC)**.

It has a **bimodal** age distributions being most common in the **young adults** (15-35 years) and **elderly** individuals (> 55 years).

Type	Frequency	Prognosis	Notes
Lymphocyte depleted	Rare	<b>Worst prognosis</b>	
Lymphocyte predominant	Around 5%	<b>Best prognosis</b>	
Mixed cellularity	Around 20%	Good prognosis	Associated with a large number of RSC.
<b>Nodular sclerosing</b>	<b>Most common</b> (around <b>70%</b> )	Good prognosis	More common in women. Associated with lacunar cells.

Hodgkin's lymphoma is associated with EBV, 25% of patients have a constitutional upset (night fever, sweats, weight loss, pruritis, lethargy).

### **Hodgkin's lymphoma: staging**

#### **Ann-Arbor staging of Hodgkin's lymphoma:**

- **I:** single lymph node.
- **II:** 2 or more lymph nodes/regions on same side of diaphragm.
- **III:** nodes on both sides of diaphragm.
- **IV:** spread beyond lymph nodes extra-nodal organs (liver, BM).

NB: **Spleen** is regarded as a **Lymph Node region**,  
So lymphoma with **splenomegaly** >>> Stage **III**

Each stage may be subdivided into A or B:

- **A** = no systemic symptoms other than pruritus.
- **B** = weight loss > 10% in last 6 months, fever > 38c, night sweats (**p**oor prognosis).

'B' symptoms also imply a **p**oor prognosis:

- 1) **Weight loss** > 10% in last 6 months
- 2) **Fever** > 38°C
- 3) **Drenching Night sweats**

**NB:** Fatigue, pruritus, LN mass size, EBV infection although they are common, **BUT** they have no prognostic significance.

Other factors associated with a **p**oor prognosis:

- 1) Male
- 2) Age > 45 years
- 3) Stage IV disease
- 4) Hb < 10.5 g/dl
- 5) Lymphocyte count < 600/μl or < 8%

- 6) WBCs > 15,000/ $\mu$ l
- 7) Albumin < 40 g/l

Diagnosis:

- Hodgkin results in patchy bone marrow infiltration, an isolated bone marrow biopsy may yield non-specific results.
- Bone marrow biopsy is more useful for staging of advanced disease.
- **Lymph node biopsy** would be more likely to be positive, **RSC** is evident on microscopy.

Management:

- Early stage (IA or IIA): Radiotherapy and chemotherapy.
- Later stage (III, IVA or IVB): Chemotherapy alone.
- Large mass in chest regardless of stage: Radiotherapy and chemotherapy.
- Chemotherapy includes **ABVD**: **Adriamycin**, **Bleomycin**, **Vincristine**, **Doxorubicin**, cyclophosphamide, prednisolone, Rituximab & others.
- Prognosis is good overall, but it depends on classification and staging.

**Bleomycin related pulmonary fibrosis** is a major toxicity of the widely used ABVD regimen. A HRCT scan and PFTs are required to diagnose this.

Also **Adriamycin** (also known as **Doxorubicin**) can cause **cardiotoxicity**, with evidence of abnormalities on the ECG & Echocardiography.

**NB: Relapsed Hodgkin lymphoma** in an **early** relapse (less than one year) must be managed aggressively with **salvage chemotherapy** followed by BEAM conditioned **autologous stem cell transplantation** as the established gold standard.

**EX:** A 25-year-old lady with a history of nodular sclerosing Hodgkin lymphoma in remission for 9 months after 6 cycles of ABVD chemotherapy presents again with a one month history of dry cough.

CXR shows mediastinal widening, and PET scanning shows active thoracic disease. Biopsy of the mediastinal mass reveals nodular sclerosing Hodgkin.

What is the most appropriate management option for this lady >>> **Salvage chemotherapy followed by autologous stem cell transplant.**

**Mantle radiotherapy** was introduced during **1960s** for people with **Hodgkin's** disease whose cancer was confined to LNs in the chest, neck or under the arms which aim to give radiotherapy to all **LN's lying above the diaphragm**.

**Women** who were treated with mantle therapy appear to be at a greater risk of developing a **breast cancer** and **hyperthyroidism** (thyroid nodules or malignancy), so they should have screen by breast MRI and TFTs.

### **Non-Hodgkin's Lymphomas (NHL)**

They are a diverse group of lymphomas that include any kind of lymphoma except Hodgkin's lymphomas.

Types of NHL vary significantly in their severity, from indolent to very aggressive.

**Low-grade lymphoma** is predominantly a disease of **older** people and is more likely to **bone marrow infiltration**.

Most of NHL are of **B cell phenotype**, although T cell tumours are increasingly being recognized.

#### **Presentation:**

- Most present with advanced disease, **bone marrow infiltration** being almost invariable.
- Anaemia, ↑ TLC and/or ↓ PLT are suggestive of Bone marrow infiltration.
- **Low grade anaemia** is a more common presenting feature versus pancytopenia.
- **Burkitt's lymphoma**
- **Extra-nodal presentation** is more common than Hodgkin's disease.
- **Renal impairment** in NHL usually occurs as a consequence of ureteric obstruction secondary to intra-abdominal or pelvic LN enlargement.

#### **Management:**

- **LN Biopsy** is sufficient for a definitive diagnosis.
- It is essential for modern classification to submit the lymphoid tissue for **immune-phenotyping** and **cytogenetics/molecular analysis**.
- **Chemotherapy** is the main stay of treatment in most cases, but carries associated **risk** of **leukaemia** which peaks around 5 years after original treatment.
- High-grade Lymphoma are responsive to chemotherapy and potentially curable.
- Low-grade Lymphoma are incurable with conventional therapy.

### **Burkitt's lymphoma**

Burkitt's lymphoma is a **high-grade B-cell neoplasm (NHL)**.

It was first discovered in children in West Africa who presented with a jaw tumour, extra-nodal abdominal involvement and ovarian tumours.

There are two major forms:

- **Endemic (African) form:** typically involves maxilla or mandible.
- **Sporadic form:** abdominal (e.g. **ileo-caecal**) tumours are **the most common form**. More common in patients with HIV.

Burkitt's lymphoma is associated with the **C-MYC gene translocation**, usually **t(8:14)** which is observed in approximately **80%** of patients with the disease.

The Epstein-Barr virus (EBV) is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.

Management is with **chemotherapy** (cyclophosphamide, vincristine, methotrexate and prednisolone).

This tends to produce a rapid response which may cause '**tumour lysis syndrome**'.

### **Maltomas**

Maltomas, also known as marginal zone lymphomas, are low grade lymphomas, most often diagnosed in the stomach.

They are peculiar in that they are often associated with chronic inflammation of some type:

- In the **stomach**, secondary to chronic **H-pylori** gastritis.
- In the **eyes**, secondary to **Sjogren's** syndrome.
- In the **thyroid**, secondary to **Hashimoto's** thyroiditis.
- In the **intestine**, secondary to **Crohn's** or **Coeliac** disease.

TTT of H-pylori will cause regression of 90% of low-grade gastric maltomas.

**Acute Tumour Lysis Syndrome (ATLS)**

Tumour lysis syndrome occurs as a result of cell breakdown following chemotherapy.

It is a common complication of haematological tumours which have a high proliferation index, for example, Burkitt's lymphoma, hyperleukocytic acute myelogenous leukaemia (AML), diffuse large B-cell lymphoma.

This releases a large quantity of intracellular components such as potassium, phosphate and uric acid.

**Association:**

- Acute leukaemia.
- High-grade NHL.
- **Pre-treatment** ↑ level of **LDH** as it correspond with tumour bulk.

**Complications:** (Like rhabdomyolysis)

- 1) **Hyperkalaemia**
- 2) **Hyperphosphataemia**
- 3) **Hyperuricaemia**
- 4) **Hypocalcaemia**
- 5) Acute renal failure

**Management:**

- Prevention by **good hydration 3 L/m<sup>2</sup>** before starting chemotherapy (about 4-6 L per day).
- Dietary modification: ↓ K in diet.
- ↑ Uricaemia → urine alkalinization and **allopurinol**.
- Osmotic diuresis is **NOT** first line therapy may contribute to precipitation of uric acid in renal tubules.
- **Rasburicase** (a recombinant version of urate oxidase, an enzyme which catalyses the conversion of uric acid to allantoin, this allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective) is often given before the chemotherapy to reduce the risk of this occurring.

<b>ATLS TTT &gt;&gt;&gt; Intravenous hydration with 3 L/m<sup>2</sup> and Rasburicase</b>
---

**Haematological malignancies: genetics**

The common **translocations** associated with haematological malignancies:

**t(9;22) - Philadelphia chromosome:**

- Present in > **95%** of patients with **CML**
- This results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22.
- The resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal.
- Also present in around **25%** of **adult ALL** cases also have this translocation.
- Poor prognostic indicator in ALL and AML.

**t(15;17):**

- Seen in **acute promyelocytic leukaemia (M3) of AML**.
- Fusion of PML and RAR-alpha genes

**t(8;14):**

- Seen in **Burkitt's lymphoma**
- **MYC** oncogene is translocated to an immunoglobulin gene

**t(11;14):**

- **Mantle cell lymphoma**
- Deregulation of the cyclin D1 (BCL-1) gene

**Myeloma: features**

Multiple myeloma is a neoplasm of the bone marrow **plasma cells**.

Myeloma is a clonal B-cell malignancy characterized by proliferation of plasma cells that accumulate mainly in bone marrow and usually secrete paraprotein.

It accounts for **1%** of all malignancies and **10%** of haematological malignancies.

The peak incidence is patients aged **60-70** years.

Multiple myeloma is a relatively common malignancy that is part of a **spectrum** of disorders ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukaemia.



Gammopathy is a disturbance in the synthesis of immunoglobulins. **Monoclonal gammopathy** suggests there is a single neoplastic clone causing an excess of immunoglobulin.

There is overproduction of immunoglobulin (Ig) usually **IgG** in about **55%**, IgA in about 20%: of these patients, 40% have Bence-Johns proteinuria. Light chain is found in 20% of patients, while IgD and IgE myeloma account for about 1% of cases.

**Hyperviscosity syndrome:** the viscosity is directly proportional to the size of the molecule causing it; therefore **IgM**, which is pentameric, is most likely to cause hyperviscosity, followed by the dimeric **IgA**, then **IgG**.

An important differential diagnosis is monoclonal gammopathy of unknown significance (MGUS).

Macroglobulins are plasma globulins of high molecular weight. They are a central feature of Waldenström macroglobulinaemia, where proliferation of lymphocytes cause an excess of IgM.

This is an important differential diagnosis when multiple myeloma is suspected.

Macroglobulins are not typically a feature of multiple myeloma.

Clinical features:

- Bone disease:
  - **Bone pain** (the commonest presenting symptom, present in **70%** of patients at time of diagnosis),
  - Osteoporosis + **pathological fractures (in up to 60% of cases)** (typically **vertebral**) and osteolytic lesions.
- **Spinal cord compression** can develop due to vertebral compression fractures or vertebral plasmacytomas >>> **Urgent MRI of the spine**.
- Lethargy
- Renal failure with proteinuria and normal sized kidneys.
- Other features: **AL amyloidosis** e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity
- Acute bacterial Infection (e.g. **pneumonia**)
- Decreased resistance to infection due to impaired humoral immunity, often compounded by leukopenia secondary to bone marrow infiltration. Patients therefore have a high prevalence of infection, especially with encapsulated organisms such as Pneumococcus.

- **Hypercalcaemia** and **hyperphosphataemia** (see below)
- The **globulin** level is **raised** (globulin level = total protein – albumin). Normal level should be below 36 g/L.
- Positive P-ANCA

**Diagnostic Criteria for myeloma** (International Myeloma Working Group 2010):  
**ALL THREE (3) are required:**

- 1) **Monoclonal plasma cells in the bone marrow** (involving **>10%** of the bone marrow) and/or presence of biopsy-proven plasmacytoma.
- 2) **Monoclonal proteins in the serum** (Plasma immunoelectrophoresis to look for an M band) and **urine** (Lambda light chains secreted in the urine as Bence Jones protein, this is most accurately detected by urine protein electrophoresis).
- 3) **Myeloma-related organ dysfunction ( $\geq 1$ ):**
  - 1)  $\uparrow$  Serum Calcium.
  - 2) Renal impairment.
  - 3) Anaemia.
  - 4) Bone lesions on the skeletal survey: lytic lesions or osteoporosis.

**Hypercalcaemia in myeloma:**

- 1) Primary factor: due primarily to **increased osteoclastic bone resorption** caused by local cytokines (e.g. IL-1, TNF) released by the myeloma cells.
- 2) Much less common contributing factors: impaired renal function, increased renal tubular calcium reabsorption and elevated **PTH-rP** levels.

**The hyperphosphataemia in multiple myeloma:**

It is due to reduced renal excretion which may be directly due to renal impairment or interference with excessive protein load.

**Myeloma: prognosis:**

- **B2-microglobulin** is a useful marker of prognosis - **raised** levels of  $>3.5$  mg/L is strongly imply poor prognosis. ☹
- **Low levels of albumin** are also associated with a poor prognosis. ☹
- Hypercalcaemia
- Severity of anaemia
- Viscosity

- LDH,
- Recurrent bacterial infections.

**International prognostic index:**

Stage	Criteria	Median survival (months)
I	B2 microglobulin < 3.5 mg/l Albumin > 35 g/l	62
II	Not I or III	45
III	B2 microglobulin > 5.5 mg/l	29

Pt e' **Renal impairment+ Hypercalcaemia+ High total protein >> Myeloma.**

**TTT:**

- **Melphalan** and prednisolone.
- Immunomodulatory drugs such as **thalidomide** and **lenalidomide**: significant improvements in survival may be expected through the addition of it to standard chemotherapeutic regimes. (SE: Teratogenic, myelosuppression, somnolence, peripheral neuropathy and constipation)
- **Bortezomib**: inhibits the 26 S proteasome, indirectly inhibiting nuclear factor Kappa and causing apoptosis.
- **Bisphosphonates** reduce bony disease in myeloma, lowering the frequency of pathological fractures. There is also evidence that bisphosphonates modulate the disease and have some anti-tumour activity. As a result, bisphosphonates should be given routinely to patients with myeloma, even in the absence of hypercalcaemia.
- **Plasma exchange**.

**MGUS (Monoclonal gammopathy of undetermined significance)**

MGUS is monoclonal paraproteinaemia without evidence of disorders such as myeloma, Waldenstrom's macroglobulinaemia and amyloidosis.

MGUS, also known as **benign paraproteinaemia and monoclonal gammopathy** is a common condition that causes a paraproteinaemia and is often mistaken for myeloma.

Differentiating features are listed below.

Patients are at increased risk of developing myeloma.

Around 1% may progress to myeloma annually. Around 10% of patients eventually develop myeloma at 5 years, with 50% at 15 years.

The vast majority of patients can be managed **conservatively**.

Evidence of deteriorating renal function or impaired immunity may indicate that transformation to myeloma has occurred.

Features:

- Usually **asymptomatic** and picked up **incidentally**.
- **No bone pain** or increased risk of infections
- **No end organ damage**
- Around 10-30% of patients have a demyelinating neuropathy

Differentiating features from myeloma:

- Normal immune function.
- **Normal beta-2 microglobulin levels.**
- **Lower level of paraproteinaemia than myeloma** (e.g. < 30g/l IgG, or < 20g/l IgA). (i.e. there is high IgG but not as high as in myeloma).
- Stable level of paraproteinaemia.
- **No** Bence John's protein in urine.
- No clinical features of myeloma (e.g. **NO lytic lesions on x-rays, NO hypercalcaemia, NO immune paresis or NO renal disease**).
- **NO evidence of end-organ damage.**
- **Plasma cell involvement of bone marrow is only Less than 10%.**

<b>Normal levels of: IgG up to 13 gm/L, IgA up to 3 gm/L &amp; IgM up to 3 gm/L</b>
---

Diagnostic criteria:

- 1) Serum paraprotein < 30 g/l , AND
- 2) In bone marrow biopsy the Clonal plasma cells < 10%, AND
- 3) NO myeloma-related organ impairment.

TTT: Regular follow up with blood tests only.

**Waldenström's macroglobulinaemia (WM)**

Waldenström's macroglobulinaemia is an uncommon condition seen in **older** men (70- 80 years). It is a type of **lymphoplasmacytoid lymphoma malignancy**.

It is characterised by the presence of a **high level of a macroglobulin (immunoglobulin M [IgM])**, elevated serum viscosity and the presence of a lymphoplasmacytic infiltrate in the bone marrow, resulting in **pancytopenia**.

Raynaud's phenomenon may herald the onset of this condition and is due to cryoglobulinaemia.

The **monoclonal IgM** causes:

- **Hyperviscosity syndrome**
- **Pancytopenia**
- Cryoglobulinaemia types 1 and 2
- Coagulation abnormalities >> DVT
- Polyneuropathies
- Cold agglutinin disease
- Primary amyloidosis
- Tissue deposition of amorphous IgM in skin, GIT, kidneys, and other organs.

Features:

- 1) Systemic upset: weight loss, lethargy (NO BONY PAINS).
- 2) **Monoclonal IgM paraproteinaemia**
- 3) **Hyperviscosity syndrome** in around 10-15% of patients e.g. visual disturbance due to **retinal vein thrombosis, DVT**.
- 4) **Hepatosplenomegaly**
- 5) **Lymphadenopathy**
- 6) **Cryoglobulinaemia** e.g. **Raynaud's**
- 7) **↑ ESR**

**Investigations:**

- **Bone marrow aspirate** usually shows infiltration with lymphoplasmacytoid cells.
- **Protein electrophoresis** shows an IgM paraprotein (> 20 gm/L).

**Death** occurs either:

- due to **cardiovascular** events because of increased viscosity, or
- due to progression of **bone marrow infiltration** leading to suppressed response to **infection**

Ex: Old male with a DVT + recently lost weight + Blood tests reveal ↑ IgM : >>> Waldenstrom's macroglobulinaemia.

EX: Old woman has a much raised IgM level, pancytopenia, Raynaud's phenomenon and a foot ulcer >>> Waldenström's macroglobulinaemia.

Waldenstrom's macroglobulinaemia is more likely than MGUS (monoclonal gammopathy of undetermined significance) (given the weight loss and deep vein thrombosis (evidence of hyperviscosity)).

IgM paraproteinaemia >>>? Waldenstrom's macroglobulinaemia.

IgG and IgA are the most common type of immunoglobulins produced in myeloma.

**Management:**

- **Alkylating agents:** is the **first** line ttt.
- Young patient may benefit from doxorubicin.
- Monoclonal antibody as rituximab, sometimes in combination with chemotherapeutic drugs: chlorambucil, cyclophosphamide or vincristine.
- Corticosteroids may be used in combination.
- **Plasmapheresis** can be used to treat the **hyperviscosity**, it can rapidly reduce viscosity and risk of thromboembolic events, but it does not address the underlying disease.

**NB:** Causes of hyperviscosity syndrome: Myeloma, Waldenström macroglobulinaemia, (PRV) Polycythaemia rubra vera & Leukaemia.

**POEMS syndrome**

It is **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal gammopathy and **S**kin changes.

It is a **rare multisystem** disease that occurs in the setting of **plasma cell dyscrasia**.

The pathophysiology of this disease is not **known**; however, elevated levels of cytokines and growth factors have been implicated.

**Polyneuropathy:** bilateral symmetric disturbance, it involves both motor and sensory nerves, begins distally and has a progressive proximal spread. Both demyelination and axonal degeneration are noted. Cranial or autonomic nerves are not involved.

**Organomegaly:** Liver, spleen & LN.

**Multiple Endocrinopathy** e.g. thyroid.

**Gammopathy:** e.g. MGUS, but classical Myeloma is not usually associated.

**Venous thromboembolism (VTE):**

General risk factors:

- Increased risk with advancing age
- Obesity
- Family history of VTE
- Pregnancy (especially **puerperium**)
- Immobility
- Hospitalisation
- Anaesthesia
- Central venous catheter: femoral >> subclavian

Underlying conditions:

- Malignancy
- Thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
- Heart failure
- Antiphospholipid syndrome

- Behcet's
- Polycythaemia
- Nephrotic syndrome
- Sickle cell disease
- Paroxysmal nocturnal haemoglobinuria
- Hyperviscosity syndrome
- Homocystinuria

Medication:

- Combined oral contraceptive pill: 3rd generation more than 2nd generation.
- HRT Hormone replacement therapy.
- Raloxifene and Tamoxifen.
- Antipsychotics especially Olanzapine (Zyprexa ®) have recently been shown to be a risk factor.

SIGN also state that the following are risk factors for **recurrent VTE**:

- Previous unprovoked VTE
- **Male sex**
- Obesity
- Thrombophilias

### Deep vein thrombosis (DVT): diagnosis and management

**Diagnosis:**

NICE guidelines 2012 relating to the investigation and management of DVT.

If a patient is suspected of having a DVT a two-level DVT **Wells score** should be performed:



**Two-level DVT Wells score**

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	2

Clinical probability simplified score:

- DVT likely: 2 points or more
- DVT unlikely: 1 point or less

If a DVT is 'likely' (2 points or more):

- A proximal leg vein ultrasound scan should be carried out within 4 hours and, if the result is negative, a D-dimer test.
- If a proximal leg vein ultrasound scan cannot be carried out within 4 hours a D-dimer test should be performed and low-molecular weight heparin administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours).

If a DVT is 'unlikely' (1 point or less)

- Perform a D-dimer test and if it is positive arrange:
- A proximal leg vein ultrasound scan within 4 hours

- If a proximal leg vein ultrasound scan cannot be carried out within 4 hours low-molecular weight heparin should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours).

**Management:**

Low molecular weight heparin (LMWH) or fondaparinux should be given initially after a DVT is diagnosed.

- A vitamin K antagonist (i.e. warfarin) should be given within 24 hours of the diagnosis
- the LMWH or fondaparinux should be continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time as warfarin until the INR is in the therapeutic range
- Warfarin should be continued for **at least 3 months**. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'
- NICE add 'consider extending warfarin **beyond 3 months** for patients with **unprovoked proximal DVT** if their risk of VTE recurrence is high and there is no additional risk of major bleeding'. This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months. In practice most clinicians give **6 months** of warfarin for patients with an unprovoked DVT/PE.
- For patient with a **second time provoked DVT** (e.g. also post-operative DVT for 2<sup>nd</sup> time) >>> warfarin for **6 months** and search for inherited thrombophilia.
- For patients with **recurrent DVT whilst on warfarin** is an indication for **life-long** anticoagulation.
- For patients with **active cancer + VTE** >>> NICE recommend using **LMWH for 6 months**. (LMWH has the advantage of being easier to reverse and stop if a cancer-related bleed occurs, for example massive haemoptysis in a patient with lung cancer).

N.B: Warfarin does not undergo extensive hepatic first-pass metabolism.
---

Venous thromboembolisms - length of warfarin treatment

- **Provoked** (e.g. recent surgery): 3 months
- **Unprovoked**: 6 months

### **Further investigations and thrombophilia screening:**

As both **malignancy** and **thrombophilia** are obvious risk factors for deep vein thrombosis NICE make recommendations on how to investigate patients with unprovoked clots.

Offer all patients diagnosed with **unprovoked DVT or PE** who are not already known to have cancer the **following investigations for cancer:**

- 1) A physical examination (guided by the patient's full history) and
- 2) A chest X-ray and
- 3) Blood tests (CBC, serum calcium and LFTs) and urinalysis.
- 4) Consider further investigations for cancer with an **abdominal-pelvic CT scan** (and a **mammogram** for women) in all patients aged over 40 years with a first unprovoked DVT or PE.

### **Thrombophilia screening:**

- Not offered if patients will be on lifelong warfarin (i.e. won't alter management)
- Consider testing for Antiphospholipid antibodies if unprovoked DVT or PE
- Consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE.

### **Thrombophilia: causes**

#### **Inherited:**

- 1) Protein C deficiency
- 2) Protein S deficiency
- 3) Antithrombin III deficiency
- 4) **Factor V Leiden mutation (FVL) (Activated protein C resistance):** The most common inherited thrombophilia.

**Acquired:**

- 1) Antiphospholipid syndrome
- 2) The OCP
- 3) PNH (paroxysmal nocturnal haemoglobinuria).
- 4) PRV (polycythaemia rubra vera).

**Thrombophilia testing is considered useful in patients presenting with:**

- 1) A first episode of venous thromboembolism (VTE) at a **young age** (usually considered **less** than **45** years of age).
- 2) **Idiopathic** venous thrombosis (so no need if the patient clearly has a provoked DVT relating to a fracture).
- 3) A **family history** of thrombosis, particularly in a **first** degree relative.
- 4) VTE in an **unusual** vascular territory.
- 5) **Neonatal purpura fulminans**.
- 6) **Warfarin** induced **skin necrosis (WISN)**.

**Protein C deficiency**

Protein C deficiency is an autosomal codominant condition which causes an increased risk of thrombosis.

Features:

- Venous thromboembolism
- **Skin necrosis** following the commencement of **warfarin (Warfarin induced skin necrosis) (WISN)**: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary paradoxical procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules (microthrombi) in the skin particularly in the adipose areas such as buttocks and breast (skin necrosis).

TTT:

- Supportive by Vit K, FFP to replace protein C level.
- Prostacyclin and protein C infusion has been trialed.
- Warfarin can be reintroduced at a lower loading dose, but recurrence can occur.

NB: Heparin induced skin necrosis can be indistinguishable from WISN, but is antibody mediated, and occurs in 5-10 days after commencing heparin, usually with the presence of heparin/platelet factor 4 antibodies.

Protein C is an inhibitor that, once activated, inhibits clot formation and enhances fibrinolysis. It is liver synthesised and vitamin K dependent. Protein C is converted to an active enzyme by a thrombin-thrombomodulin complex on the endothelial cell surface.

Activated protein C inhibits a plasminogen activator inhibitor, which results in enhanced fibrinolysis, and, with protein S as a co-factor, inhibits the clotting of the activated factors 5 and 8 by limited proteolysis. Activated protein C thus controls the conversion of factor 10 to 10a and prothrombin to thrombin.

**EX:** Pt with DVT and has started enoxaparin 1 mg/kg BID and warfarin 10 mg >>> on the **2<sup>nd</sup> day**, there is **black lesions** over the **buttocks** with **normal platelet count** >>> **WISN**, the most likely diagnosis is **protein C deficiency**.

#### **Activated protein C resistance (Factor V Leiden mutation) (FVL)**

Activated protein C resistance is **the most common inherited thrombophilia**.

It is due to a mutation in the Factor V Leiden gene.

It is caused by an amino acid substitution that impairs the ability of activated protein C and S to inactivate factor Va.

It is mostly inherited in an **autosomal dominant** fashion and is present in **5-9%** of the **European** population but is rare in people of Asian and African descent.

About **5%** of the **UK** population carry a factor 5 Leiden mutation.

Heterozygotes have a 5-fold risk of venous thrombosis whilst **homozygotes** have a **50-fold** increased risk.

Cascade screening of adult family members is appropriate and members who carry FVL can receive lifestyle counselling regarding contraception and long journeys.

Women who take the OCP however have a significantly raised risk of venous thrombosis and currently the use of any type of OCP in women with confirmed factor 5 Leiden mutation is not recommended.

**General population screening is not practical or cost-effective** at present, but **screening of patients with relatives known** to be affected is recommended, if a mutation is **found** then **stop OCP** and **non-hormonal contraception** should be recommended unless a woman has completed her family and expresses a preference for **sterilization**.

Factor V Leiden mutation results in >> activated **protein C resistance**

Any white patient < 45 years old with thrombotic event, should make you think of factor V Leiden mutation.

**EX:** Female 30 years old on OCP with 1st time acute DVT and thrombophilia screen revealed that she has factor V Leiden mutation >>> **Warfarin for 6 months (NOT lifelong).**

Recent population analysis / case series have now suggested that **the risk benefit for lifelong warfarin** in a patient with factor V Leiden mutation who has a **first DVT** may not be positive due to bleeding risk, as such lifelong warfarin is **no longer recommended** in this situation for a **first** event.

**N.B:**

**Activated protein C resistance (Factor V Leiden)** >> is the most common inherited thrombophilia.

**Von Willebrand's disease**>>is the most common inherited bleeding disorder.

### **Antithrombin III (AT 3) deficiency**

Antithrombin III deficiency is an inherited cause of thrombophilia occurring in approximately 1:2,000 of the population. Inheritance is **autosomal dominant**.

Antithrombin III (AT3) is a plasma inhibitor protein that blocks the enzymatic activity of some serine proteases coagulation factors. The activity of this inhibitor is increased by heparin.

Antithrombin III inhibits several clotting factors, primarily thrombin, factor X and factor IX. It mediates the effects of heparin.

Heparin works by binding to antithrombin III, enhancing its anticoagulant effect by inhibiting the formation of thrombin and other clotting factors. **Patients with antithrombin III deficiency** may therefore be **resistant to heparin treatment**.

AT3 is synthesised by the **liver**, is **not** vitamin K dependent, and can be **consumed** during **DIC**.

Normal newborns have a reduced activity.

Antithrombin III deficiency comprises a heterogeneous group of disorders, with some patients having a deficiency of normal antithrombin III whilst others produce abnormal antithrombin III.

Patients with **nephrotic** syndrome >>> **loss of AT 3 in urine** >>> ↑ risk of thrombosis (DVT/PE).

Features:

- **Recurrent venous thrombosis**
- Arterial thrombosis do occur but is uncommon

Management:

- 1) Thromboembolic events are treated with **lifelong warfarinisation**.
- 2) Heparinisation during pregnancy.
- 3) Antithrombin III concentrates (often using during surgery or childbirth).

**NB:** As patients with antithrombin III deficiency have a degree of resistance to heparin, so **anti-Xa levels** should be monitored carefully to ensure adequate anticoagulation by the LMWH.

### **Pregnancy: DVT/PE**

Overview:

- Pregnancy is a hypercoagulable state
- Majority occur in last trimester

Pathophysiology:

- Increase in factors VII, VIII, X and fibrinogen
- Decrease in protein S
- Uterus presses on IVC causing venous stasis in legs

Management:

- Warfarin contraindicated
- S/C LMWH preferred to IV heparin (less bleeding and thrombocytopenia).

**Antiphospholipid syndrome (APL Syndrome)**

Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thrombosis, recurrent fetal loss and thrombocytopenia.

It may occur as a primary disorder or secondary to other conditions, most commonly SLE.

A key point for the exam is to appreciate that Antiphospholipid syndrome causes a **paradoxical rise in the APTT**. This is due to an ex-vivo reaction of the lupus anticoagulant autoantibodies with phospholipids involved in the coagulation cascade.

**APLS >>> (paradoxically) prolonged APTT + low platelets ± (low TLC in SLE)**

These are a heterogenous group of approximately **20 autoantibodies** directed against phospholipid binding plasma proteins.

Three of the most clinically important are:

- 1. The anticardiolipin antibodies.**
2. The lupus anticoagulant.
3. Anti-beta-2 glycoprotein I antibodies (anti-β2GPI antibodies).

Antibodies should be demonstrated on **at least 2 occasions separated by 12 weeks**.

**Features:**

- 1) Venous/arterial thrombosis**
- 2) Recurrent fetal loss:** (loss of 3 or more consecutive pregnancies)
- 3) Thrombocytopenia**
- 4) Prolonged APTT**
- 5) Livedo reticularis**
- 6) Other features: pre-eclampsia, pulmonary hypertension

Antiphospholipid syndrome may be **primary**, or **secondary associated** with other conditions such as SLE, other autoimmune disorders, lymphoproliferative disorders, phenothiazines (rare).



**Antiphospholipid antibody syndrome (APAS) can be diagnosed if:**

- The patient has **anticardiolipin antibodies**, or **lupus anticoagulant** on **two occasions**, over a period of **12 weeks**,

**And either:**

- Has had a **thrombus**, or
- A history of **recurrent < 10 week** pregnancy loss, **or one** pregnancy loss **> 10 weeks** in gestation when other causes of pregnancy loss have been excluded.

**Management - based on BCSH guidelines:**

- **Initial venous** thromboembolic events: evidence currently supports use of warfarin with a target INR of 2-3 for 6 months.
- **Recurrent venous** thromboembolic events: lifelong warfarin; **if** occurred whilst taking warfarin then increase target INR to 3-4.
- **Arterial** thrombosis is for ttt with lifelong warfarin with target INR 2-3.

The occurrence of **even a single thrombotic** event in a patient with **Antiphospholipid syndrome** warrants **lifelong** anticoagulation, as the risk of **recurrence** is **20-70%**.

**LMWH** should be used initially whilst loading **warfarin**.

In general, it is recommended that the **INR** is maintained **above 2.0**, although a **higher level (above 3)** may be indicated for patients with recurrent thrombosis on treatment.

Anticoagulation to prevent foetal loss remains controversial.

**Antiphospholipid syndrome in pregnancy:**

In pregnancy the following complications may occur:

- Recurrent miscarriage
- IUGR
- Pre-eclampsia
- Placental abruption
- Pre-term delivery
- Venous thromboembolism

**Management:**

- **Low-dose aspirin** should be commenced **once** the pregnancy is confirmed on urine testing.
- **Low molecular weight heparin once** a fetal heart is seen on ultrasound. This is usually **discontinued** at 34 weeks gestation.
- These interventions increase the live birth rate **7-fold**.
- This combination has been showed to lead to a **70%** live birth rate in future pregnancies.

<b>Antiphospholipid syndrome in pregnancy &gt;&gt;&gt; Aspirin + LMWH</b>
---

**Heparin**

There are two main types of heparin - unfractionated, 'standard' heparin or low molecular weight heparin (LMWH).

Heparin works by binding to antithrombin III then forms a complex which enhancing the antithrombin III anticoagulant effect by inhibiting the formation of thrombin and other clotting factors IXa, Xa, XIa and XIIa (9,10,11,12).

Patients with antithrombin III deficiency may therefore be resistant to heparin treatment.

LMWH however only increases the action of antithrombin III on factor Xa.

Both UFH and LMWH can cause **hyperkalaemia**. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose may be reversed by **protamine sulphate**, although this only partially reverses the effect of LMWH.

Heparin resistance may be due to **Antithrombin III deficiency**.

The table below shows the differences between standard heparin and LMWH:

	Standard heparin (UFH)	Low molecular weight heparin (LMWH)
<b>Administration</b>	Intravenous	Subcutaneous
<b>Duration of action</b>	Short	Long
<b>Mechanism of action</b>	Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, XIa and XIIa	Activates antithrombin III. Forms a complex that inhibits factor Xa
<b>Side-effects</b>	Bleeding. HIT. Osteoporosis.	Bleeding. Lower risk of HIT and osteoporosis.
<b>Monitoring</b>	Activated partial thromboplastin time (APTT)	<b>Anti-Factor Xa</b> (although routine monitoring is not required)
<b>Notes</b>	Useful in situations where there is a high risk of bleeding as anticoagulation can be terminated rapidly.	Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes.

**Protamine sulphate** is the **antidote** for LMWH.

This reverses most, but not all, of the effects of LMWH.

The dose of protamine sulphate given is dependent upon the dose of LMWH administered and the time of administration.

If protamine is given **within 8 hours** of the LMWH then a maximum neutralising dose is **1 mg** protamine/**100 units (or 1 mg)** of LMWH given in the last dose.

If **more than 8 hours** have passed since the dose of LMWH was given, administer **0.5 mg** protamine per **100 units (or 1 mg)** of LMWH given.

Protamine is administered by **slow IV infusion** (over **10 minutes**) to avoid a hypotensive reaction. Protamine requires a high level of caution when being prescribed and administered.

**Rivaroxaban (Xarelto ®):** is a highly selective direct factor Xa inhibitor.

**Inhibition of factor Xa** interrupts the intrinsic and extrinsic pathway of the coagulation cascade, inhibiting both thrombin formation and development of thrombi.

Rivaroxaban does not inhibit thrombin and that it has no effect on platelets has been demonstrated.

Indications: chronic non-valvular AF.

### **Heparin-induced thrombocytopenia (HIT):**

It is a severe **Immune mediated** drug reaction that can occur in any patient exposed to **any form heparin** either UFH or LMWH also either by therapeutic or prophylactic doses or even the minute amounts in heparin flushes and on heparin-coated catheters.

**Antibodies** usually develop after a patient has been on heparin for 5 or more days, but may develop sooner if there has been previous heparin exposure.

Usually does not develop until after 5-10 days of treatment.

Despite being associated with low platelets, bleeding is rare. HIT is strongly associated with **thrombosis**. HIT is actually a **prothrombotic** condition (DVT, PE, MI, CVS, limb artery occlusion).

Features include a greater than 50% reduction in platelets (e.g. from 490 to 200x10<sup>9</sup>/L), thrombosis and skin allergy.

### **Types:**

- **Type I HIT:**

- It is a non-immune condition and usually occurs within 48-72 hrs post commencing heparin
- PLT rarely < 100. PLT return to normal over 4 days
- There is no ↑ risk of thromboembolism.
- TTT: continue the LMWH ttt and observe

- **Type II HIT:**

- It is much rarer, and also known as HIT with thrombosis, and usually occurs 5-10 days after starting heparin,
- PLT usually < 100 to about 50.

- Pt. is at ↑ risk of thromboembolic events.
- TTT: Heparin products should be stopped and the patient commenced on alternative medication.

### **Diagnosis (is clinical):**

1. PLT < 100 or < 50% of from the patient's baseline.
2. Exclude other causes of thrombocytopenia.
3. Resolution of thrombocytopenia after cessation of heparin.
4. Supportive lab test: **HIT Abs (Anti-heparin platelet factor 4 antibody)** by functional tests (more specific) and immunoassays.

Functional tests: which measure PLT activity in the presence of the patient's serum and heparin, it includes:

- Heparin Induced Platelet Aggregation (HIPA).
- Serotonin Release Assay (SRA).

### **Treatment:**

- **Stop** all forms of heparin.
- Options of **alternative anticoagulants** which do not react with HIT antibodies, such as lepirudin, danaparoid and Argatroban.
- The heparinoid **Danaparoid** (a combination of heparin and dermatan sulphate) appears to be the drug of choice for acute treatment and prophylaxis because of its low placental permeability especially in **pregnant** patient.
- Hirudin is a direct thrombin inhibitor that is approved for treatment of patients with HIT.
- Other direct thrombin inhibitors: Bivalirudin and Argatroban.
- **Hirudin** should only be used when there is either cross-reactivity with heparin-induced antibodies or cutaneous allergy against heparinoids.
- **Warfarin should NOT** be initiated for longer term protection from further events until substantial platelet count recovery has occurred.
- HIT patients who are switched to warfarin alone after the discontinuation of heparin may paradoxically have worsening thrombosis and develop venous limb gangrene and skin necrosis.

**EX:** A 28-year-old pregnant woman is being treated for a DVT with unfractionated heparin. A recent blood test shows low platelets 35 ×10<sup>9</sup>/L (N= 150-400). The best course of action for this woman is >>> **Stop heparin** and alternative anticoagulation should be started **Danaparoid**.

## Warfarin

Warfarin is an oral anticoagulant which inhibits the reduction of vitamin K to its active hydroquinone form, which in turn acts as a cofactor in the carboxylation of vitamin K dependent clotting factor **II, VII, IX and X** (mnemonic = **1972**) and **protein C**.

**Warfarin >>> Inhibition** of vitamin K **epoxide reductase enzyme**, which is an enzyme that converts vitamin K to its active form (hydroquinone).

Indications:

- 1) **Venous thromboembolism**: target INR = **2.5**, (if recurrent 3.5)
- 2) **Atrial fibrillation**, target INR = 2.5
- 3) **Mechanical heart valves**, target INR depends on the valve type and location. Mitral valves generally require a higher INR than aortic valves.

Patients on warfarin are monitored using the **INR** (international normalised ratio), the ratio of the prothrombin time for the patient over the normal prothrombin time.

Warfarin has a long half-life and achieving a stable INR may take several days. There a variety of loading regimes and computer software is now often used to alter the dose.

Factors that may potentiate warfarin (i.e. ↑ INR):

- 1) **Liver** disease.
- 2) P450 enzyme **inhibitors**, e.g.: amiodarone, ciprofloxacin >> ↑ INR.
- 3) Drugs which displace warfarin from plasma albumin, e.g. **NSAIDs**.
- 4) Inhibit platelet function: NSAIDs
- 5) **Cranberry juice** (عصير التوت البرى)
- 6) **Antibiotics** that kill intestinal flora >> ↓ Vit K absorption >> ↑ INR.
- 7) **Metronidazole** and **co-trimoxazole** inhibit the clearance of the active S isomer of warfarin, therefore enhancing its anticoagulant effect.

**Clopidogrel** does not appear to have a clinically relevant effect on the pharmacokinetics or pharmacodynamics of warfarin. However, its the concurrent use with warfarin, increases the bleeding risk.

Side-effects:

- 1) Haemorrhage
- 2) **Teratogenic**, although can be **used in breast-feeding mothers**
- 3) **Skin necrosis**: when warfarin is first started biosynthesis of protein C is reduced. This results in a **temporary procoagulant state** after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis.
- 4) Purple toes

**Dentistry in warfarinised patients >>> check INR 72 hours before procedure, proceed if INR < 4.0**

The BNF gives specific advice with regards to this, in the section 'Prescribing in dental practice'. If a patient has a history of an **unstable INR** then it should be **checked within 24 hours of the dental procedure**.

Warfarin is teratogenic and should be stopped before the 6<sup>th</sup> week of pregnancy to minimise the risk of fetal abnormalities.

So any female on warfarin and ask for conception and pregnancy >>> **either** stop warfarin immediately and replace with LMWH (the ideal solution) **or** continue warfarin but change to LMWH within 6 weeks of conception (the more practical solution because less good compliance with injections of LMWH).

**EX:** A 60-year-old female with a mitral valve replacement (MVR) and (AF) on warfarin is due for extensive abdominal surgery.

What is the most appropriate therapy as regards her anticoagulation >>> **Stop warfarin 5 days pre-operatively, bridge therapy with LMWH and give vitamin K if INR is still above 3.0 on eve of operation.**

The most appropriate bridging therapy in this case is LMWH, with the last dose being given **not less than 24 hours prior to the procedure**, the warfarin having been discontinued five days prior to the procedure.

**NB:** Warfarin should never be given alone, without heparin, when starting for treating a thrombotic event. This is because when warfarin is started, there is a **pro-thrombotic state** created, by **falling protein C and protein S** (these are **vitamin K dependent natural anticoagulants**) and these fall **before** factors II, VII, IX and X.

### Warfarin overdose

An update of the BCSH (British Committee for Standards in Haematology) guidelines emphasised the preference of **prothrombin complex concentrate (PCC)** over FFP in major bleeding.

PCC is product of choice for **warfarin reversal** in the setting of **active bleeding** and a **markedly raised INR**.

**PCC** with Vit K is used if there is **major bleeding** corresponding to **1500-2000 ml** or **> 30%** of blood volume loss.

**PCC (factors II, VII, IX, and X) 30-50 units/kg.**

If PCC is **unavailable**, **FFP 15 mL/kg** can be given (but is less effective).

Vit K IV is **slower** in onset than other options of (PCC, FFP & Factor 7 VIIa) and also it may make the patient resistant to re-dosing with warfarin (**difficult re-warfarinisation**) and at increased risk of thrombo-embolic events at a later stage, but in practise this is not a major problem.

Vit K dosage is 1-5 mg oral or 0.5-1 mg IV.

<b>Major bleeding</b>	<b>1) Stop warfarin.</b> <b>2) Give Vitamin K 5mg IVI.</b> <b>3) PCC - but if it is not available so, FFP.</b>
<b>INR &gt; 8.0</b> <b>Minor bleeding</b>	Stop warfarin, restart when INR < 5.0 Give intravenous vitamin K 1-3mg Repeat dose of vitamin K if INR still too high after 24 hours
<b>INR &gt; 8.0</b> <b>No bleeding</b>	Stop warfarin, restart when INR < 5.0 Give vitamin K 1-5mg by mouth, using the IV preparation orally Repeat dose of vitamin K if INR still too high after 24 hours
<b>INR 5.0-8.0</b> <b>Minor bleeding</b>	Stop warfarin, restart when INR < 5.0 Give intravenous vitamin K 1-3mg



<b>Major bleeding</b>	<b>1) Stop warfarin.</b> <b>2) Give Vitamin K 5mg IVI.</b> <b>3) PCC - but if it is not available so, FFP.</b>
<b>INR 5.0-8.0</b> <b>No bleeding</b>	Withhold (omit) 1 or 2 doses of warfarin, then review INR Reduce subsequent maintenance dose

As FFP can take time to defrost, **prothrombin complex concentrate (PCC)** should be considered in cases of intracranial haemorrhage. It is used in such an urgent situation. The use of PCC is currently limited by availability.

EX: Pt with AF on warfarin, presented with DCL and intracranial haemorrhage. The most appropriate management is >> **Vit K IV + (PCC).**

Due to his warfarin therapy he will have reduced levels of factors II, VII, IX and X and requires **replacement** to correct his INR rapidly. This is most effectively achieved by the administration of **prothrombin complex concentrate (PCC)** (Beriplex or Octaplex ®, 25-50 units/kg IVI).

These result in **complete reversal of the warfarin-induced anticoagulation within 10 minutes** but the clotting factors have a finite half-life and therefore **5 mg IV vitamin K** should be given at the same time.

Vit K will start to affect the INR within 4-8 hours.

PCC is plasma derived, so there is a potential risk of transfusion-transmitted infection and it is prothrombotic.

Fresh frozen plasma (**FFP**) contains more dilute clotting factors and therefore produces **inferior** correction and should **not** be used in the management of life threatening bleeding (unless PCC is not available).

FFP contains low level of coagulation factors and it is estimated that even at a dose of 15 ml/kg, level of most factors will only approach 20% of normal.

**FFP may not completely reverse the effects of warfarin so is NOT recommended in many local guidelines.** البلازما موضة قديمة ليس لها استخدام حديثاً

Cryoprecipitate and oral vitamin K are not recommended for the management of life threatening bleeding.

Cryoprecipitate, recombinant factor VII and platelets are not indicated for warfarin reversal.

The rate of fatal haemorrhage in patients receiving warfarin approaches 1%.

**EX:** A 70-yrs-old male is admitted with **hematemesis**. He is currently being treated with warfarin for AF and his **INR is 10**. What is the most appropriate immediate treatment of his INR > **Prothrombin complex concentrate (PCC)**.

### **Thrombocytopenia**

#### **Causes of severe thrombocytopenia:**

- 1) **ITP**
- 2) **TTP**
- 3) **DIC**
- 4) **Haematological malignancy**

#### **Causes of moderate thrombocytopenia:**

- 1) HIT (Heparin induced thrombocytopenia).
- 2) Drug-induced (e.g. quinine, diuretics, sulphonamides, aspirin, thiazides)
- 3) Alcohol
- 4) Vit. B12 deficiency
- 5) Liver disease
- 6) Hypersplenism
- 7) Viral infection (EBV, HIV, hepatitis)
- 8) Pregnancy
- 9) SLE/Antiphospholipid syndrome

#### **Drug-induced thrombocytopenia (probable immune mediated):**

- **Heparin**
- **NSAIDS**
- **Quinine**
- **Abciximab**
- **Diuretics:** furosemide, thiazides
- **Antibiotics:** Penicillins, Sulphonamides, Rifampicin
- **Anticonvulsants:** Carbamazepine, Valproate

**Idiopathic thrombocytopenic purpura (ITP):**

ITP is an immune mediated reduction in the platelet count.

Antibodies are directed against **the glycoprotein IIb-IIIa** or Ib-V-IX complex.

Common cause of death is **bleeding** (mainly **intracranial**).

Over recent years a **familial propensity** for the development of ITP has been identified, although the particular gene susceptibility is yet to be identified.

ITP can be divided into acute and chronic forms:

Acute ITP:

- More commonly seen in children
- Equal sex incidence
- May follow an infection or vaccination
- Usually runs a self-limiting course over 1-2 weeks

Chronic ITP:

- More common in young/middle-aged women
- Tends to run a relapsing-remitting course

Evan's syndrome:

- ITP in association with autoimmune haemolytic anaemia (AIHA).

Investigations:

- 1) **Antiplatelet autoantibodies (usually IgG).**
- 2) **Blood film shows occasional giant platelets:** The bone marrow is still working as there are giant platelets seen on film, which you see when there is peripheral consumption of the platelets.
- 3) **Bone marrow aspiration** shows ↑ megakaryocytes in the marrow, this should be carried out prior to the commencement of steroids in order to rule out leukaemia.

In ITP >>> The most important investigation is a **blood film**, although not diagnostic, this will confirm the CBC findings and also exclude more sinister pathology such as leukaemia.

Management:

- 1) **Oral prednisolone (80% of patients respond): prednisolone 60 mg daily.**
- 2) IVIG immunoglobulins.
- 3) Immunosuppressive drugs e.g. cyclophosphamide.
- 4) Splenectomy if platelets < 30 after 3 months of steroid therapy.
- 5) Platelet stimulating factors are under development; these are expected to play role in future management.

Isolated thrombocytopenia in a well patient >>> points to a diagnosis of ITP.
---

**The management of ITP post-splenectomy:**

- **Exclusion** of accessory splenic tissue by imaging studies
- **Confirming** post-splenectomy changes (Howell-Jolly bodies and target cells) on blood film examination.
- **Thrombopoietin** agonists (eltrombopag or romiplostim).
- **Immunosuppressant** agents like: Cyclosporine, MMF and Rituximab.

<p><b><u>NB:</u></b> The management of (ITP) which presents with a <b>catastrophic bleed</b> is aimed at achieving a <b>rapid rise in platelet count</b> to reduce the morbidity &gt;&gt;&gt; <b><u>Methylprednisolone pulse IV + IVIG and platelet transfusion.</u></b></p>
--

Although platelet transfusions are not efficacious in ITP (due to transfused platelets being consumed in the same way as platelets released from bone marrow), they are useful in this setting, together with high doses of intravenous steroids and immunoglobulins.

**EX:** Male pt. 33 years old with ITP (PLT 3), he is commenced on prednisone 1 mg/kg/day. On the 3rd day of his admission, he is noted to be hemiparetic. Urgent CT scanning of the brain shows a massive intracerebral haemorrhage with no midline shift >>> TTT: **Methylprednisolone pulse IV + IVIG and platelet transfusion**, together with **consideration for urgent craniotomy** and intracranial clot evacuation by neurosurgeons.

**Thrombotic thrombocytopenic purpura (TTP)**

TTP is life-threatening multi-system disorder characterised by **pentad**.

TTP is a **clinical diagnosis** and potential diagnosis in any patient with anaemia and thrombocytopenia - **95%** of cases are **fatal** if left untreated.

Symptoms are usually non-specific.

High index of suspicion is necessary to make the diagnosis.

Renal and neurological dysfunctions are the main complications.

The survival rate has improved from about 3% prior to the 1960s to 85% now.

Pathogenesis:

- 1) Abnormally large and sticky multimers of **von Willebrand's factor** cause platelets to clump within vessels.
- 2) In TTP there is a **deficiency of ADAMTS13** (a metalloprotease enzyme) which breakdowns large multimers of von Willebrand's factor.
- 3) **Overlaps** with haemolytic uraemic syndrome (**HUS**). (**see nephrology**)

Features: (Typically **adult females**): **Pentad (5)**:

- 1) **Microangiopathic haemolytic anaemia (MAHA)**: by peripheral smear fragmented RBCs (schistocytes).
- 2) **Thrombocytopenia with purpura.**
- 3) **Neurological** abnormalities (microemboli in microcirculation): (usually more marked in TTP than in HUS). Neurological manifestations are present in most patients, and range from confusion and severe headache, to focal neurological abnormalities, seizures and coma.
- 4) **Renal failure** (usually less marked in TTP than in HUS).
- 5) **Fever**

<b>Not all of the above (pentad) may be present.</b>
--

<b>In practice, the triad of schistocytes, thrombocytopenia and ↑ LDH are sufficient to make the diagnosis.</b>
---

<b>Low platelets PLUS Neuro signs and purpura &gt;&gt;&gt; point towards TTP/HUS</b>
--

As an aide-memoire, this can be remembered as (**TTP- PENTAD**):

**P** - Pyrexia

**E** - Endothelial damage

**N** - Neurological abnormality

**T** - Thrombocytopenia

**A** - Anaemia (MAHA)

**D** - Damage to kidney.

Other features are:

- Purpura, ecchymosis, and menorrhagia due to thrombocytopenia may also be seen in 20% of cases.
- Peripheral digit ischaemic syndrome.
- Non-occlusive mesenteric ischaemia.
- Adult respiratory distress syndrome (ARDS).

Livedo reticularis is not commonly seen in TTP. It occurs more commonly in conditions such as Antiphospholipid syndrome and cholesterol embolism

Additional laboratory findings:

- The reticulocyte count is generally elevated.
- LDH and bilirubin are often elevated as markers of haemolysis.
- **Direct Coombs' test** should be **negative** to **rule out** AIHA.
- **Normal clotting factors (PT & PTT)** should be **normal** to **rule out** DIC.
- Assays have been developed to measure **von Willebrand factor cleaving enzyme (ADAMTS-13) activity**. ADAMTS-13 activity can be **low**, and inhibitors to its activity can often be demonstrated in patients with TTP.

Causes:

- Post-infection e.g. urinary, gastrointestinal
- Post BMT in AML.
- Malignant hypertension
- Pregnancy

- Eclampsia, post-partum acute renal failure.
- Drugs: cyclosporine, OCP, penicillin, clopidogrel (Plavix), acyclovir.
- Tumours (adenocarcinoma).
- SLE, Vasculitis, collagen vascular disease (scleroderma), cryoglobulinaemia.
- HIV.

**NB: Causes of MAHA include:**

- Thrombotic thrombocytopenic purpura (**TTP**)
- Haemolytic uraemic syndrome (**HUS**)
- Disseminated intravascular coagulation (**DIC**)
- Haemolysis by **prosthetic** heart valves
- **Malignant hypertension**
- **Pre-eclampsia**
- **HELLP** - haemolysis elevated liver enzymes and low platelets.
- **Septicaemia**
- **Vasculitis**
- **Connective** tissue disease (polyarteritis nodosa [**PAN**], **Wegener's**, systemic lupus erythematosus [**SLE**]).

**NB: The differential diagnosis is a pregnancy associated thrombotic microangiopathy, which includes:**

- Thrombotic thrombocytopenia purpura (TTP)
- Haemolytic uraemic syndrome (HUS)
- Disseminated Intravascular coagulation (DIC)
- Pre-eclampsia
- HELLP
- Acute fatty liver of pregnancy
- Systemic lupus erythematosus (SLE).

**Management:**

- **Urgent Plasmapheresis:** Plasma exchange with **FFP (not Albumin)** (to replace the missing factor in TTP, called ADAMTS-13) is the ttt of choice.
- Steroids, Immunosuppressants: Vincristine
- Rituximab can be used.
- **No antibiotics** - may worsen outcome.
- Platelets transfusion is **contraindicated** in TTP as it has negative impact on prognosis unless mandatory indicated if with haemorrhage. The pathological

basis relates to micro-thrombi formation which results in ischaemia in affected blood vessels with ensuing end-organ damage (neurological, renal and cardiac).

**TTP >>> urgent plasma exchange with FFP** is first-line ttt

**TTP in pregnancy** typically occurs **early in pregnancy** - usually less than 24 weeks, whereas HELLP and pre-eclampsia occur usually much later.

The only management option for **TTP in pregnancy is plasma exchange**. Delivery has **no** effect on disease.

**NB:** Tranexamic acid is sometimes misused for bleeding in TTP, but it is prothrombotic and may be worsening the condition, hence it should be stopped in TTP.

**NB:** TTP can occur in **less than 1%** of patients receiving **clopidogril** or ticlopidine >>> **peripheral blood film >>> fragmented RBCs**.

**EX:** Pt after 2 weeks from PCI and Plavix usage, develop Rt. sided weakness, bleeding tendency, low platelets, anaemia, renal impairment, fever, Disturbed LOC with confusion >>> **TTP due to clopidogril**.

### **DIC (Disseminated Intravascular Coagulation)**

DIC is a complex systemic thrombo-haemorrhagic disorder involving the generation of intravascular fibrin and the consumption of procoagulants and platelets.

DIC is caused by the enhanced and abnormally **sustained generation of thrombin**, and is associated **with elevated products of fibrin breakdown**, one of these being **↑ D-dimer** and **↑FDPs**.

In a recent review by Yu and colleagues, the combination of the **D-dimer** and the **FDP** assay provides **the most rapid** and **specific** diagnosis of DIC.

**Organ failure** is a common finding, being as common as **bleeding** in DIC, and is likely to be due to fibrin deposition within the organ.

Secondary bursts of thrombin formation seen in DIC are instigated by the **intrinsic pathway**.



DIC is associated with the following:

- 1) Falling platelet count,
- 2) Prolonged PT,
- 3) Prolonged PTT
- 4) Decreased fibrinogen,
- 5) ↑FDPs
- 6) ↑ D-Dimer.
- 7) ↓ Protein C - reduced
- 8) ↓ Antithrombin - reduced.
- 9) Associated **MAHA** (Microangiopathic haemolytic anaemia): usually complicate **chronic** rather than acute DIC, it is due to mechanical damage to RBCs from fibrin strands present within the circulation.

But **the clotting factors may be normal**, especially when one considers that the **acute phase response** may shorten the activated partial thromboplastin time (APTT) and increase fibrinogen.

So Normal clotting parameters **don't** effectively **exclude** a diagnosis of DIC.

The presence of DIC significantly increases **mortality** rates in affected patients

Treatment of the underlying cause, for example, sepsis, **does not always lead** to resolution of the condition. ☹

**Where there is no bleeding or thrombosis, blood products are not recommended**, since there is no evidence base for their use, and they expose the patient unnecessarily to the risks of transfusion.

Transfusion of platelets or plasma components in patients with DIC should **not** be primarily based on laboratory results and should in general be reserved for patients who present with **bleeding**. Hence the most useful parameter for deciding whether this patient requires active treatment would be the **presence or absence of bleeding**.

Where there is bleeding, blood products should be used to gain haemostasis.

**TTT: Blood products replacements:**

- **Cryoprecipitate** (Fibrinogen replacement infusion): (If Fibrinogen <1)
- **PLT TX:** (Only If PLT count < 50)
- **FFP:** (If PT and PTT > 1.5 upper limit)
- **PRBCs**

As a general rule, ttt with blood products in DIC is **not indicated unless** life-threatening **bleeding** occurs or if an invasive procedure is planned.

**To correct a coagulopathy you need to aim for:**

- Fibrinogen >1.0 g/L >>> by TX of **Cryoprecipitate**.
- Platelets >50 ×10<sup>9</sup>/L >>> by TX of **PLT**.
- PT and APTT <1.5 upper range of normal >>> by TX of **FFP**.

**EX:** pregnant female with **abortion** and severe vaginal bleeding, **Low PLT** 70 ×10<sup>9</sup>/L, **prolonged PT** 25 sec, **prolonged PTT** 55 sec, **low fibrinogen** 0.5 g/L (N= 2-4) >>>> **DIC** >>>> **Cryoprecipitate** (Fibrinogen replacement infusion).

**When bleeding** is the major problem, the aim is to maintain the prothrombin and activated thromboplastin time **at a ratio of 1.5 times of the control** and the **fibrinogen level above 1 g/L**.

**EX:** A 26-year-old woman presented at 35 weeks of pregnancy with profuse vaginal bleeding. She had suffered two previous miscarriages.

She had a pulse of 95 bpm, BP 110/84 mmHg and no fetal heart sounds were audible.

Lab: ↓Hb **9**, ↓PLT **66**, ↑PT **22**, ↑PTT **55**, ↓Fibrinogen **0.5** (N= 2-4 gm/L).

This is **DIC** >>> TTT: **Cryoprecipitate (Fibrinogen replacement infusion)**.

When bleeding is the major problem, the aim is to maintain the PT and PTT at a ratio of 1.5 times of the control and the fibrinogen level above 1 g/L.

Platelet transfusion is recommended if the count is less than 50 ×10<sup>9</sup>/L.

Anaemia is not very severe so in this case fibrinogen replacement would be the appropriate first choice with blood transfusion an addition if bleeding continues and patient develops hypovolaemic shock.

The commonest cause of **chronic DIC** in an **elderly** man with **prostatic** symptoms is **prostate cancer**, the presence of immature red (nucleated RBCs) and white (metamyelocytes and myelocytes) cells in the blood is known as **leucoerythroblastic blood film**, and is often seen in cases of bone marrow invasion and is relatively frequently present in **metastatic prostatic cancer**, particularly hormone-resistant case.

**EX:** Old male 80 years has easy bruising, loss of weight, jaundice, prostatism, Lab: TLC 11, Hb 8, PLT 55, prolonged PTT, low fibrinogen, blood film shows fragmented schistocytes, nucleated RBCs, metamyelocytes and myelocytes >>> The most likely diagnosis is **chronic DIC due to prostate cancer**.

### Von Willebrand's disease (vWD)

It is **the most common inherited bleeding disorder**.

The vWF gene is located near the tip of the short arm of chromosome 12.

The majority of cases are inherited in an **autosomal dominant** fashion and characteristically behaves **like a platelet disorder** i.e. epistaxis and menorrhagia are common whilst haemarthroses and muscle haematomas are rare.

Males and females are equally affected, although the disease manifestations are more obvious in the females due to menstruation and the associated menorrhagia.

Role of von Willebrand factor (vWF):

- 1) Large glycoprotein which forms up to 1,000,000 Da in size. رجل ضخيم
- 2) Promotes platelet adhesion to damaged endothelium مستر فون خدام للصفائح
- 3) Carrier molecule for factor VIII. مستر فون خدام لفأكتور ثمانية

Types of vWD:

- 1) **Type 1:** partial quantitative deficiency in vWF (**80%** of patients) (**most common**).
- 2) Type 2: qualitative deficiency (abnormal form) of vWF.
- 3) Type 3: total deficiency (lack) of vWF (autosomal recessive) (**most severe**).

Investigation:

- 1) Prolonged bleeding time.
- 2) **APTT** may be prolonged/slightly prolonged (in **50%** of patients).
- 3) **Factor VIII** levels may be mild/moderately reduced (much ↓ in haemophilia A)
- 4) vWF levels: are variable and can be influenced by a number of factors, therefore a single level of vWF within the normal reference range does not exclude the diagnosis of vWD.
- 5) **vWF antigen level** concentration in plasma: detected by quantitative immunoassay or ELISA, it is variably reduced, and also can be normal.
- 6) **vWF activity assay**: the degree of platelet agglutination is proportional to the concentration of vWF in the plasma, it is reduced in vWD.
- 7) Defective platelet aggregation with ristocetin: Ristocetin is an antibiotic that causes vWF to bind to and activate platelets, platelets rapidly agglutinate in

response to ristocetin but the presence of vWF is necessary for this reaction to occur.

- 8) New test: **PFA-100**: it has 95% sensitivity to diagnose VWD.

To assess the **bleeding tendency** pre procedure for patient with von Willebrand's disease (vWBD), the most useful test in practice is to do the **vWF antigen and activity**; but you would also do **plasma F VIII c activity**.

Management:

- 1) **Tranexamic acid (Cyclokapron ®)**: It is anti-fibrinolytic drugs for mild bleeding.
- 2) **Desmopressin (DDAVP) (Vasopressin)**:
  - It may be given to increase the amount of the vWF long enough for surgery or dental procedures to be performed.
  - It can provide a 2 fold to 5 fold increase in plasma vWF and factor VIII concentrations.
  - It induces cAMP-mediated vWF secretion by a direct effect on endothelial cells (from Weibel-Palade bodies in endothelial cells).
  - It is similar to ADH, so SE is hyponatraemia.
- 3) For severe disease or prior to major surgery (like appendectomy): you would use a **von Willebrand factor concentrate (Humate-P®)**, i.e. **intermediate purity (vWF rich) factor VIII**, which contains the highest concentration of vWF. (**NOT** factor VIII concentrate).

**NB:** Intermediate purity factor VIII (containing high amount of vWF)

High purity factor VIII (containing lower amount of vWF)

So Purified or recombinant preparations are avoided since they contain only small concentrations of vWF.

**NB:** Factor VIII concentrate, cryoprecipitate, FFP (should be avoided when possible to minimise the risk of transfusion acquired viral illnesses).

**EX:** A 14-year-old boy presents with excessive bleeding from a tooth cavity following an extraction at the dentist.

His investigations show: CBC: normal, PT: normal, slightly elevated PTT 45 sec (N= 30-40), slightly low Factor VIII 45 U/dL (N= 50-150).

The most likely diagnosis is >>> **vWD**

Factor VIII is only slightly reduced in vWD as von Willebrand factor is a protective carrier for factor VIII.

**NB: In haemophilia A >> there is much less factor VIII and much more prolonged PTT than described in VWD.**

**EX:** Pt known to have type 1 von Willebrand's disease will have a tooth extraction >> the most appropriate management to reduce the risk of bleeding is >> **Desmopressin (DDAVP) and tranexamic acid.**

**EX:** A 21-year-old lady diagnosed with severe type 1 von Willebrand disease is planned to undergo emergency appendectomy >>> **Intermediate purity factor VIII.**

## Haemophilia

Haemophilia is an **X-linked recessive** disorder of coagulation.

Up to 30% of patients have no family history of the condition.

Haemophilia <b>A</b>	<b>X-linked</b> genetic disorder due to deficiency of factor <b>VIII (8)</b> and represents <b>90%</b> of Haemophilia cases.
Haemophilia <b>B</b> (Christmas disease)	<b>X-linked</b> genetic disorder due to deficiency of factor <b>IX (9)</b> . It is <b>more severe</b> but <b>less common</b> than Haemophilia A, it represent about <b>20%</b> of Haemophilia cases. .
Haemophilia <b>C</b>	<b>Autosomal recessive</b> genetic ( <b>NOT X-Linked</b> ), due to deficiency of factor <b>XI (11)</b> . It is not completely recessive so heterozygous individuals also shows ↑ bleeding.

Features:

- **Haemarthroses**, haematomas
- Prolonged bleeding after surgery or trauma

Blood tests:

- **Prolonged APTT**
- With **NORMAL** bleeding time, thrombin time and prothrombin time.

Up to 10-15% of cases with haemophilia A develop antibodies to factor VIII treatment

**NB:** Prolonged APTT may be caused by (4):

- Heparin therapy,
- Von Willebrand's disease (vWD), or
- Haemophilia A or B or acquired factor 8 VIII deficiency,
- Antiphospholipid syndrome.

Haemophilia is an X-linked recessive disorder and would hence be expected **only** to occur in **males**. With exception that only appears in **female** patient if with **Turner's syndrome** **only have one X chromosome** however, they may develop X-linked recessive conditions.

**EX:** A 45-year-old man is to undergo knee surgery. He has a history of **factor IX deficiency**. You are concerned about the prospect of significant bleeding during surgery.

What is most likely to reduce his risk of bleeding >> **Tranexamic acid**.

**Tranexamic acid competitively** inhibits activation of plasminogen, thereby **reducing the conversion of plasminogen to plasmin**.

This results in slower degradation of fibrin clots, fibrinogen and other plasma proteins including factors V and VIII.

As such it may be of value in **patients undergoing surgery** who have inherited **factor IX deficiency** in order to reduce the perioperative risk of bleeding.

**Recombinant factor IX** is of course also an option where it is available, although patients have a high tendency to form neutralising antibodies to factor IX.

**NB:** Vasopressin (Desmopressin) is associated with a significant increase in levels of both factor VIII and von Willebrand factor in haemophilia A. Any increase seen in factor IX levels after vasopressin is however much more minor. As such tranexamic acid is a much more useful therapeutic choice.

### **Factor VII (7) Deficiency**

It is **very rare**, it is inherited as an autosomal recessive fashion, and tends to cause **mild to moderate** bleeding disorder.

Factor 7 is the only factor unique to the **PT** (prothrombin time).

Factor 7 deficiency >>> **prolonged PT** with **normal PTT**.

TTT: factor replacement with FFP or recombinant activated factor VII.

**Acquired Haemophilia**

It is associated with **anti-factor VIII IgG antibodies** and is **idiopathic** in the majority of cases.

**Association:**

- Autoimmune disease: RA or IBD
- Drugs: Phenytoin

**Management:**

- Factor **VIII** replacement.
- Immunosuppressive: steroids ± steroid sparing agents as cyclosporine.

**EX:** Male patient 65 years old with spontaneous haematoma in his right thigh, with past medical history of RA, Labs are normal apart from mild prolonged PTT >>> **acquired haemophilia**.

Haemophilia A or B or VWD would not present de-novo at the age of 65.

**Acquired Factor VIII (8) Deficiency**

It results from the development of **inhibitors** against factor **VIII** coagulation factor. It occurs mainly in **elderly** or during pregnancy, often in association with concurrent **autoimmune** disease or **malignancy**.

**Bleeding** can be **severe** to the point that great care should be taken with cannula insertion since compartment syndrome may ensure.

**Association:**

- 1) Malignancy
- 2) Autoimmune disorders: Psoriasis & Pemphigus
- 3) Drugs: penicillins, cephalosporins

**Diagnosis:**

- 1) Bleeding tendency.
- 2) **Prolonged PTT** (Intrinsic pathway).
- 3) PTT doesn't correct/will only correct **slightly** with adding of **FFP**.
- 4) **Factor VIII inhibitor** is detected.
- 5) Bethesda titre can quantify the inhibitor.
- 6) There is 20% mortality rate.

**Treatment:**

- 1) Recombinant Factor VIII replacement is usually ineffective as the inhibitors have rapid activity.

- 2) **Recombinant activated factor VII 7 (rFVIIa)** has been successfully used in patients with acquired haemophilia. It binds to the surface of activated platelets, where it supports thrombin generation and bypass the need for FVIII.
- 3) **Factor Eight Inhibitor Bypassing Agent (FEIBA):** It is a pooled donor product has a mix of several other activated clotting factors which bypass the factor VIII requiring step in the coagulation pathway, and is prothrombotic, causing MI and DIC in a subset of patients.
- 4) Definitive removal of the auto-antibody by immunosuppression is successful in at least 50% of patients, but carries significant morbidity and mortality in elderly.

<p><b>EX:</b> Old male 70 years with severe epistaxis from both nostrils, Hb 7, ESR 75, normal PT, prolonged PTT, low factor VIII <b>8</b> level &gt;&gt;&gt;&gt; <u>Acquired Factor VIII (8) Deficiency</u> &gt;&gt;&gt; TTT: <u>Recombinant activated factor VII 7 (rFVIIa)</u>.</p>
--

### **Hereditary haemorrhagic telangiectasia (HHT)**

Also known as **Osler-Weber-Rendu syndrome**.

It is a multisystem vascular dysplasia characterised by the presence of multiple arteriovenous malformations (**AVMs**) that lack intervening capillaries and result in direct connections between arteries and veins.

It is an **autosomal dominant** condition characterised by (as the name suggests) multiple telangiectasia (Small AVMs) over the skin and mucous membranes often rupture and bleed.

About 20% of cases occur spontaneously without prior family history.

May present as iron deficiency anaemia secondary to GIT bleeding.

#### **There are 4 main diagnostic criteria (The Curacao criteria):**

- 1) **Epistaxis:** spontaneous, recurrent nose bleeds.
- 2) **Telangiectases:** multiple at characteristic sites (lips, oral cavity, fingers, nose).
- 3) **Visceral lesions:** for example gastrointestinal telangiectasia (with or without bleeding which most commonly begins after age 50 years), pulmonary arteriovenous malformations AVM in 30%, hepatic AVM in 30%, cerebral AVM in 20%, spinal AVM.
- 4) **Family history:** a first-degree relative with HHT.



If the patient has **2** >> so they are said to have a **possible** diagnosis of HHT.

If they meet **≥ 3** >> so they are said to have a **definite** diagnosis of HHT.

N.B:

Condition	Bleeding time	PT	PTT	Notes
Vit K Def.	Unaffected	Prolonged	Prolonged	1 normal
Haemophilia	Unaffected	Unaffected	Prolonged	1 affected
DIC	Prolonged	Prolonged	Prolonged	All affected

Factors	PT	PTT
7 (Extrinsic pathway)	Prolonged	Unaffected
2 – 5 – 10	Prolonged	Prolonged
8 – 9 – 11 – 12 (Intrinsic pathway)	Unaffected	Prolonged

**NB:** Prolonged APTT may be caused by (4): heparin therapy, haemophilia A or B or acquired factor 8 deficiency, von Willebrand's disease, or Antiphospholipid syndrome.

### Thrombocytosis

Thrombocytosis is an abnormally high platelet count, usually  $> 400 \times 10^9/L$ .

**Thrombopoietin** is the key hormone in the regulation of megakaryocyte differentiation.

The most common cause of thrombocytosis is a **reactive thrombocytosis**.

Causes of thrombocytosis:

- 1) **Reactive:** platelets are an acute phase reactant - platelet count can increase in response to stress such as an exercise, severe infection or surgery.

- 2) **Essential** thrombocytosis, or as part of **another myeloproliferative** disorder such as chronic myeloid leukaemia (CML) or polycythaemia rubra Vera (PRV).
- 3) **Malignancy**.
- 4) **Hyposplenism**.

### **Essential thrombocytosis (ET):**

Essential thrombocytosis is one of the **myeloproliferative** disorders which overlaps with CML, PRV and Myelofibrosis.

Megakaryocyte proliferation results in an overproduction of platelets.

In essential thrombocytosis low risk patients have a risk of thrombosis similar to that of the age and sex-matched population and a very low risk of life-threatening bleeding, **supporting close observation** as the most sensible approach.

Generally the prognosis is extremely **good** in ET with survival of over two decades expected.

Features:

- 1) Platelet count  $> 600 \times 10^9/l$ .
- 2) Both **thrombosis** (venous or arterial) and **haemorrhage** can be seen.
- 3) A characteristic symptom is a **burning sensation in the hands**.
- 4) A **JAK2 kinase (V617F mutation)** is found in around **50%** of patients.

There are a number of adverse prognostic markers for (ET): ☹

- **Age above 60**
- **Symptomatology** - particularly **thrombosis** and
- **Platelet count above 1500**.

Management:

- 1) **Hydroxyurea (Hydroxycarbamide 500 mg Capsule)** is widely used to reduce the platelet count.
- 2) Low-dose aspirin may be used to reduce the thrombotic risk.
- 3) Interferon- $\alpha$  is also used in younger patients.
- 4) Anagrelide is a second line drug in ET and has been associated with increased bone marrow fibrosis.

**EX:** A 60-year-old female presents with a platelet count of **768** ×10<sup>9</sup>/L (150 - 400). On examination she has **isolated mild splenomegaly >>> myeloproliferative disorder >>>> Bone marrow biopsy with molecular studies >>> TTT: ASA+ Hydroxyurea.**

## **Myelofibrosis**

Overview:

- A **myeloproliferative disorder**.
- Thought to be caused by **hyperplasia of abnormal megakaryocytes**.
- The resultant release of platelet derived growth factor (PDGF) is thought to stimulate fibroblasts.
- Haematopoiesis develops in the liver and spleen.

Hyperplasia of megakaryocytes → ↑ PDGF → stimulates fibroblasts

Features:

- e.g. **elderly** person with symptoms of anaemia e.g. **fatigue** (the most common presenting symptom)
- **Massive splenomegaly**
- Hypermetabolic symptoms: weight loss, night sweats etc.

Laboratory findings:

- **Anaemia**
- **High** WBC and platelet count **early** in the disease,
- But **leukopenia** and **Thrombocytopenia** are seen in **progressive** disease.
- **'Tear-drop' poikilocytes on blood film.**
- Unobtainable bone marrow biopsy - 'dry tap' therefore trephine biopsy needed.
- High urate and LDH (reflect increased cell turnover).

**Myelodysplasia (Myelodysplastic syndrome (MDS))**

It occurs mainly in **elderly** about **70-80** years old.

Transformation into **AML** occurs in around **30%** of patients.

Presentation: due to **pancytopenia**: Anaemia, Infection and Bleeding

**Median survival is 2 years.**

Patients are more likely to have **serious infections** or **life-threatening bleeds** than blastic transformation.

Few patients require aggressive therapy and most need **only supportive care**. As the vast majority are elderly patients with other medical conditions, excessive intervention is unwarranted.

Old patient with lethargy and pancytopenia >>> Myelodysplasia
---

Investigations:

- CBC: bone marrow failure, **small blasts**
- Bone marrow: ↑ cellularity, **ring sideroblasts**.

The disease can be classified into the following subtypes (WHO) 2008:

- 1) Refractory anaemia with unilineage dysplasia- i.e. anaemia, neutropenia or thrombocytopenia (<5% blasts).
- 2) Refractory anaemia with ring sideroblasts (<5% blasts; >15% sideroblasts)
- 3) Refractory anemia with multilineage dysplasia (based on bone marrow dysplasia in 2 or more myeloid lineages).
- 4) Refractory anaemia with excess blasts-1(5-9% blasts) and refractory anemia with excess blasts -2 (10-19%).
- 5) Myelodysplasia unclassified.
- 6) Myelodysplasia with isolated 5qdel (cytogenetic abnormality with prognostic significance).

If much Blasts > 20% is now classified as acute myeloid leukaemia ( <b>AML</b> ).
---

Managements:

- 1) < 5% blasts in bone marrow → conservative
- 2) ↑ TLC → “Gentle” chemotherapy
- 3) < 60 years old → “Intensive” chemotherapy
- 4) Anaemia: PRBCs transfusion + iron chelation with Desferrioxamine SC.

**Haematological malignancies: infections**

Viruses:

- **EBV:** Hodgkin's and Burkitt's lymphoma, nasopharyngeal carcinoma and HIV-associated CNS lymphomas.
- **HTLV-1:** Adult T-cell leukaemia/lymphoma.
- **HIV-1:** High-grade B-cell lymphoma.

Bacteria:

- **Helicobacter pylori:** gastric lymphoma (MALT)

Protozoa

- **Malaria:** Burkitt's lymphoma

**Neutropenia**

It is defined as an absolute peripheral blood neutrophil count of  $<2 \times 10^9 /L$ .

There is a racial variation: black and Middle Eastern people may have neutrophil count of  $< 1.5 \times 10^9 /L$  normally.

Congenital neutropenia:

- Kostmann's syndrome
- Chediak-Higashi syndrome
- Schwachmann-Diamond syndrome
- Cyclical neutropenia

Acquired neutropenia:

- **Infection:** viral: influenza, HIV, hepatitis and Bacterial sepsis.
- **Drugs:** phenytoin, carbimazole, chlorpromazine, cotrimoxazole, ACEI.
- **Immune-mediated:** SLE, Felty's syndrome (RA + splenomegaly + neutropenia).
- **Bone marrow failure:** leukaemia, lymphoma, haematinic deficiency.
- **Splenomegaly** by any cause.

Investigations:

- Blood film.
- Haematinics: factors that  $\uparrow$  Hb (Fe, TIBC, Vit B12, Folic acid, Vit D).
- Autoimmune profile.
- Bone marrow aspirate/trephine: if there is severe or prolonged neutropenia or features suggestive of bone marrow failure.

### Neutropenic sepsis (Febrile neutropenia)

Neutropenic sepsis is a relatively common complication of cancer therapy, usually as a consequence of chemotherapy.

It may be defined as a **neutrophil count of  $< 0.5 \times 10^9$**  in a patient who is having anticancer treatment and has one of the following:

- A temperature higher than 38°C or
- Other signs or symptoms consistent with clinically significant sepsis.

Prophylaxis:

- If it is anticipated that patients are likely to have a neutrophil count of  $< 0.5 \times 10^9$  as a consequence of their treatment they should be offered a fluoroquinolone.

Management:

- Antibiotics must be started immediately, do not wait for the WBC
- NICE recommend starting empirical antibiotic therapy with piperacillin with tazobactam (**Tazocin**) **immediately**.
- Many units **add vancomycin** if the patient has central venous access but NICE do not support this approach.
- Following this initial treatment patients are usually assessed by a specialist and risk-stratified to see if they may be able to have outpatient treatment.
- If patients are still febrile and unwell after 48 hours **an alternative antibiotic such as meropenem is often prescribed +/- vancomycin**.
- If patients are not responding after 4-6 days the Christie guidelines suggest ordering **investigations for fungal infections** e.g. HRCT, Aspergillus PCR etc. to determine the likelihood of systemic fungal infection, **rather than just starting therapy antifungal therapy blindly**. (For the purposes of the exam however the answer is often to give antifungals empirically).
- There may be a role for **G-CSF** in selected patients.

Neutropenic sepsis ttt >>> Tazocin + Gentamycin ± Vancomycin ± Antifungal

**EX:** In **AML** (TLC **250,000**, Hb 5, PLT 25,000) although the white cell count is **elevated**, functionally the patient is **still neutropenia** and the case should still be managed as **febrile neutropenia** >>> TTT: **Fluid resuscitation** + blood and urine **cultures** followed by **piperacillin/tazobactam + gentamicin**.

**NB:** In patients who are **prone to invasive fungal infections** it is **no** longer suggested that empirical therapy with systemic antifungals is commenced (British Committee for Standards in Haematology guidelines).

**Serological** and/or **imaging/biopsy** should be sought **prior** to instituting antifungal therapy, but imaging would be the least invasive and most easily available modality of choice in order to investigate a suspected fungal infection.

#### **Drug-induced pancytopenia**

- 1) Cytotoxics
- 2) Antibiotics: Trimethoprim, Chloramphenicol
- 3) Anti-rheumatoid: Gold, Penicillamine
- 4) Carbimazole (It causes both agranulocytosis and pancytopenia)
- 5) Anti-epileptics: Carbamazepine
- 6) Sulphonylureas: tolbutamide

#### **Aplastic anaemia: management**

- 1) **Supportive:** Blood products & prevention and treatment of infection.
- 2) **Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG):** Prepared in animals (e.g. rabbits or horses) by injecting human lymphocytes. It is highly allergenic and may cause serum sickness (fever, rash, arthralgia), therefore steroid cover usually given.
- 3) **Immunosuppression:** such as **cyclosporine** may also be given.
- 4) **Stem cell transplantation:** allogeneic transplants have a success rate of up to 80%

#### **Hyposplenism**

Causes:

- 1) **Splenectomy**
- 2) **Sickle-cell**
- 3) **SLE**
- 4) **Coeliac disease, dermatitis herpetiformis (HLA DR3).**
- 5) **Graves' disease**
- 6) **Amyloid**

Features:

- **Howell-Jolly bodies**
- Siderocytes

### Blood films: typical pictures

#### Hyposplenism e.g. post-splenectomy

- Target cells
- Howell-Jolly bodies (DNA remnant)
- Pappenheimer bodies (Siderotic granules)
- Acanthocytes

#### Iron-deficiency anaemia

- Target cells
- 'Pencil' poikilocytes
- If combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells

#### Megaloblastic anaemia

- Hypersegmented neutrophils

#### Myelofibrosis:

- 'Tear-drop' poikilocytes

#### Intravascular haemolysis

- Schistocytes

Pathological red cell forms	Associated condition(s)
Target cells	Sickle-cell/thalassaemia Iron-deficiency anaemia Hyposplenism Liver disease
'Pencil' poikilocytes	Iron deficiency anaemia
hypersegmented neutrophils	Megaloblastic anaemia
'Tear-drop' poikilocytes	Myelofibrosis



Spherocytes	Hereditary spherocytosis Autoimmune hemolytic anaemia
Basophilic stippling	Lead poisoning Thalassaemia
Howell-Jolly bodies	Hyposplenism
Heinz bodies	G6PD deficiency Alpha-thalassaemia
Schistocytes ('helmet cells')	Intravascular haemolysis Mechanical heart valve Disseminated intravascular coagulation
Burr cells (echinocytes)	Uraemia Pyruvate kinase deficiency
Acanthocytes	Abetalipoproteinemia

**EX:** Blood film with **Howell-Jolly bodies** and **pencil cells** (i.e. hyposplenism + IDA) both are seen in **Coeliac disease**

### Stains & reagents used in Haematology

Tartrate Resistant Acid Phosphatase (TRAP)	Hairy cell leukaemia
Sudan black B stain and myeloperoxidase	AML
Terminal Deoxynucleotide Transferase Stain (TDT)	ALL
Leukocyte Alkaline Phosphatase (LAP)	↑ in Leukaemoid reaction, PRV and Myelofibrosis.  ↓ in CML.

**Eosinophilia**

Causes of eosinophilia may be divided into pulmonary, infective and other.

**Pulmonary causes:**

- 1) Asthma
- 2) Allergic Broncho pulmonary aspergillosis
- 3) Churg-Strauss syndrome
- 4) Löffler's syndrome
- 5) Tropical pulmonary eosinophilia
- 6) Eosinophilic pneumonia
- 7) Hypereosinophilic syndrome

**Infective causes:**

- Schistosomiasis
- Nematodes: Toxocara, Ascaris, Strongyloides
- Cestodes: Echinococcus

**Other causes:**

- Drugs: sulfasalazine, nitrofurantoin
- Psoriasis/eczema
- Eosinophilic leukaemia (very rare)
- Cholesterol embolization
- Hodgkin's Lymphoma
- Addison's disease
- Eosinophilic Oesophagitis
- Eosinophilic Colitis.

Mnemonic: Causes of Eosinophilia is <b>NA ACCP</b> : <b>N</b> eoplasia, <b>A</b> ddison Disease, <b>A</b> sthma/ <b>A</b> llergy, <b>C</b> ollagen Vascular disease, <b>C</b> holesterol emboli, <b>P</b> arasites.
---

### Tumour markers

Tumour markers may be divided into:

- 1) Monoclonal antibodies against carbohydrate or glycoprotein tumour antigens.
- 2) Tumour antigens.
- 3) Enzymes (alkaline phosphatase, neurone specific enolase).
- 4) Hormones (e.g. calcitonin, ADH).

It should be noted that tumour markers usually have a low specificity.

#### Monoclonal antibodies:

Tumour marker	Association
CA 125	Ovarian cancer
CA 19-9	Pancreatic cancer
CA 15-3	Breast cancer

#### Tumour antigens:

Tumour marker	Association
Prostate specific antigen (PSA)	Prostatic carcinoma
Alpha-feto protein (AFP)	Hepatocellular carcinoma, <b>teratoma</b>
Carcinoembryonic antigen (CEA)	Colorectal cancer
S-100	Melanoma, schwannomas
Bombesin	Small cell lung carcinoma, gastric cancer, neuroblastoma

**Ex:** female pt. with ovarian mass with pleural effusion, ascites and ↑ CA 125 >>> **Meig's syndrome** = an ovarian fibroma assoc. with a pleural effusion and ascites.

**EX:** A 34-year-old man is reviewed four years after having an **Orchidectomy** for a **testicular teratoma**. What are the most useful follow-up investigations to detect disease recurrence? >> **Alpha-fetoprotein + beta-HCG**.

## Cancer in the UK

### The most common causes of cancer in the UK are as follows\*

- 1) Breast
- 2) Lung
- 3) Colorectal
- 4) Prostate
- 5) Bladder
- 6) Non-Hodgkin's lymphoma
- 7) Melanoma
- 8) Stomach
- 9) Oesophagus
- 10) Pancreas

### The most common causes of death from cancer in the UK are as follows:

- 1) Lung
- 2) Colorectal
- 3) Breast
- 4) Prostate
- 5) Pancreas
- 6) Oesophagus
- 7) Stomach
- 8) Bladder
- 9) Non-Hodgkin's lymphoma
- 10) Ovarian

\*excludes non-melanoma skin cancer

**N.B:**

Between 5 and 10% of all breast cancers are thought to be hereditary. Mutation in the BRCA1 and BRCA2 genes also increase the risk of ovarian cancer.

For colorectal cancer around 5% of cases are caused by hereditary non-polyposis colorectal carcinoma (HNPCC) and 1% are due to familial adenomatous polyposis.

Women who have HNPCC also have a markedly increased risk for developing endometrial cancer - around 5% of endometrial cancers occur in women with this risk factor.

**Colorectal cancer: screening****Overview:**

- Colorectal cancer is the **third** most common cancer in the **UK**, with approximately 30,000 new cases in England and Wales per year.
- The lifetime risk of developing colorectal cancer in the United Kingdom is **5%**.
- Most cancers develop from adenomatous polyps.
- Screening for colorectal cancer has been shown to reduce mortality by 16%.
- The NHS now has a national screening programme offering screening every 2 years to all men and women aged 60 to 69 years. Patients aged over 70 years may request screening.
- Eligible patients are sent faecal occult blood (FOB) tests through the post.
- Patients with abnormal results are offered a colonoscopy.
- CEA (Carcinoembryonic antigen) may be used to monitor for recurrence in patients post-operatively or to assess response to treatment in patients with metastatic disease.

**At colonoscopy, approximately:**

- 5 out of 10 patients will have a normal exam.
- 4 out of 10 patients will be found to have polyps which may be removed due to their premalignant potential.
- 1 out of 10 patients will be found to have cancer.

Colorectal cancer screening >>> PPV of FOB = **5 - 15%**.

**EX:** A 62-year-old man is called for review after a positive FOB test done as part of the national screening programme. During counselling for colonoscopy he asks what percentage of patients with a positive FOB test have colorectal cancer. What is the most accurate answer? >>> **5-15 %**

There is also a 30-45% chance of having an adenoma with a positive FOB test

### **Bladder cancer: risk factors**

The following factors are associated with the development of bladder cancer:

- **Smoking**
- Occupational: **Aniline** dyes used in printing and textile industry, **rubber** manufacture
- **Schistosomiasis**
- Drugs: **cyclophosphamide**

### **Gastric cancer**

Epidemiology:

- Overall incidence is decreasing, but incidence of tumours arising from the cardia is increasing
- Peak age = 70-80 years
- More common in males, 2:1
- More common in Japan, China, Finland and Colombia than the West

Associations:

- H. pylori infection
- Blood group **A**: **gAstric cAncer**
- Gastric adenomatous polyps
- Pernicious anaemia
- Smoking
- Diet: salty, spicy, nitrates
- May be negatively associated with duodenal ulcer

Investigation:

- Diagnosis: endoscopy with biopsy
- Staging: CT or **endoscopic ultrasound (EUS)** - endoscopic ultrasound has recently been shown to be superior to CT

N.B: <b>Gastric adenocarcinoma</b> >> Biopsy shows: <b>Signet ring cells</b>
--

### **Oesophageal cancer**

Until recent times oesophageal cancer was most commonly due to a squamous cell carcinoma but the incidence of adenocarcinoma is rising rapidly.

**Adenocarcinoma** is now the most common type of oesophageal cancer and is more likely to develop in patients with a history of gastro-oesophageal reflux disease (GORD) or Barrett's.

The majority of tumours are in **the middle third of the oesophagus**.

Risk factors:

- Smoking
- Alcohol
- GORD
- Barrett's oesophagus
- Achalasia
- Plummer-Vinson syndrome
- Rare: coeliac disease, scleroderma

Oesophageal <b>adenocarcinoma</b> is associated with GORD or Barrett's.
---

Metaplastic columnar epithelium would be seen with Barrett's <u>but</u> this is not consistent with the <u>obstructive</u> lesion seen on endoscopy.
--

### **Thymoma**

It is **the most common tumour of the anterior mediastinum**, associated with:

- 1) **Myasthenia gravis** (30-40% of patients with thymoma).
- 2) **Red cell aplasia.**
- 3) **Dermatomyositis**
- 4) Also : SLE, **SIADH**

Causes of death:

- Compression of airway
- Cardiac tamponade

### **Superior vena cava (SVC) obstruction**

It is an **oncological emergency** caused by compression of the SVC.

It is most commonly associated **with lung cancer**.

Features:

- **Dyspnoea** is the most common symptom
- Swelling of the face, neck and arms - conjunctival and periorbital oedema may be seen
- Headache
- Visual disturbance
- Pulseless jugular venous distension

Causes:

- Common malignancies: small cell lung cancer, lymphoma.
- Other: metastatic seminoma, Kaposi's sarcoma, breast cancer.
- Aortic aneurysm
- Mediastinal fibrosis
- Goitre
- SVC thrombosis

Management:

- General: Dexamethasone, balloon venoplasty, stenting
- Small cell: chemotherapy + radiotherapy
- Non-small cell: radiotherapy



Any Pt with malignancy or even disseminated malignancy and unknown primary, presents with oedema of the arms and face, persistent headache, with dilated neck veins >>> you suspect superior vena cava obstruction (SVCO).

Up to 4% of patients with lung cancer will develop SVCO at some point during their disease. Up to 10% of SCLC will present with SVCO.

**Both Non-small** cell cancer and **small** cell malignancy may cause SVCO.

SVCO is much more likely to be associated with **right sided lung lesion** 4 times than with left sided lesions.

**SVCO >>> It is an oncological emergency.**

CXR is abnormal in around 85% of cases, mediastinal widening is common.

Mediastinal radiotherapy leads to **symptomatic relief** in **80% of patients**, although case studies have shown this does not always correlate to patency of the superior vena cava.

Radiotherapy is useful but its effects are **not quick** enough.

If possible, an attempt should be made to obtain a **tissue diagnosis**, as some tumours respond to radiotherapy whereas others are more sensitive to chemotherapy.

Tumours which are very chemosensitive, such as germ cell and lymphoma, can cause SVCO.

**Dexamethasone IV** at **high** dose is of benefit in **severe** cases of SVCO + **LMWH**.

It is important to note that in 2004 NICE recommended considering **stenting** in the majority of cases of SVCO. This is a **minimally invasive** procedure which **relieves** symptoms **quicker than** chemotherapy or radiotherapy.

**SVCO >>> immediate management >>> Dexamethasone IV + LMWH.**

## Cytotoxic agents

Alkylating agents:

Cytotoxic	Mechanism of action	Adverse effects
<b>Cyclophosphamide</b>	Alkylating agent - causes cross-linking in DNA.	<ul style="list-style-type: none"> <li>➤ <b>Haemorrhagic cystitis:</b> (Incidence reduced by the use of <b>hydration</b> and <b>mesna</b>),</li> <li>➤ <b>Transitional cell carcinoma.</b></li> <li>➤ <b>Myelosuppression.</b></li> </ul>

Cytotoxic antibiotics:

Cytotoxic	Mechanism of action	Adverse effects
<b>Bleomycin</b>	Degrades preformed DNA.	<b>Lung fibrosis</b>
<b>Doxorubicin</b>	Stabilizes DNA-topoisomerase II complex. Inhibits DNA & RNA synthesis.	<b>Cardiomyopathy (DCM)</b>

Antimetabolites:

Cytotoxic	Mechanism of action	Adverse effects
<b>Methotrexate</b>	Inhibits dihydrofolate reductase and thymidylate synthesis.	Myelosuppression, mucositis, liver fibrosis, lung fibrosis
Fluorouracil (5-FU)	Pyrimidine analogue inducing cell cycle arrest and apoptosis by blocking thymidylate synthase (works during S phase)	Myelosuppression, diarrhoea, mucositis, dermatitis
6-	Purine analogue that is activated by	Myelosuppression

Cytotoxic	Mechanism of action	Adverse effects
mercaptopurine	HGPRTase, decreasing purine synthesis	
Cytarabine	Pyrimidine antagonist. Interferes with DNA synthesis specifically at the S-phase of the cell cycle and inhibits DNA polymerase	Myelosuppression, ataxia

**NB:** Capecitabine is an **orally** administered **prodrug** which is enzymatically converted to 5-fluorouracil (5FU) in the tumour.

#### Acts on microtubules:

Cytotoxic	Mechanism of action	Adverse effects
<b>Vincristine,</b> Vinblastine	Inhibits formation of microtubules, <b>mitosis</b> inhibitor ( <b>M</b> stage of cell cycle)	<b>Vincristine: Peripheral neuropathy</b> (reversible), paralytic ileus (UB atony, hesitancy). Vinblastine: myelosuppression
<b>Docetaxel (Taxanes)</b>	Prevents microtubule <u>depolymerisation</u> & <u>disassembly</u> , decreasing free tubulin.	Neutropenia, peripheral neuropathy

#### Other cytotoxic drugs:

Cytotoxic	Mechanism of action	Adverse effects
<b>Cisplatin</b>	Causes <u>cross-linking</u> in DNA	<u>Ototoxicity</u> , <b>Peripheral neuropathy</b> , <u>Hypomagnesaemia</u>
Hydroxyurea (hydroxycarbamide)	Inhibits ribonucleotide reductase, decreasing DNA synthesis	Myelosuppression

**EX:** A 60-year-old man who is currently receiving chemotherapy for non-small cell lung cancer presents for review. He is currently being treated with oral calcium supplements as hypocalcaemia was detected during a recent admission. Which one test may help determine why his **calcium level remains low despite calcium supplementation** >> **serum Magnesium** >>> **Cisplatin**, often used in the management of **non-small cell lung cancer**, is a well-known cause of **magnesium deficiency**. Without **first correcting magnesium levels it is difficult to reverse hypocalcaemia**. Whilst measuring the parathyroid hormone level is always useful it is likely to be elevated unless the patient has coexistent hypoparathyroidism.

### **5-FU:**

**Dihydropyrimidine dehydrogenase (DPD)** is the enzyme responsible for the breakdown of 5-FU. A **pharmacogenetic** disorder has been described concerning cancer patients with a **complete or partial deficiency of DPD**. In this they suffer **severe toxicity**, like new onset florid **diarrhoea**, **severe oral mucositis** and even including **death**, following the administration of 5-FU. It is similar to the picture seen with an overdose of 5-FU and is recognized in approximately 3% of patients.

### **Chemotherapy side-effects: nausea and vomiting**

Nausea and vomiting are common side-effects of chemotherapy. Risk factors for the development of symptoms include:

- Anxiety
- Age less than 50 years old
- Concurrent use of opioids
- The type of chemotherapy used

For patients at low-risk of symptoms then drugs such as metoclopramide may be used first-line.

For high-risk patients then **5HT3 receptor antagonists** such as **ondansetron** are often effective, **especially if combined with dexamethasone**.

### **Post cranial irradiation somnolence syndrome (SS)**

It was first identified in patients treated with radiotherapy for scalp ringworm infection.

It is characterised by **excessive somnolence**, **lethargy** and **clumsiness** and tends to occur around **11-21** or **31-35 days** after high dose cranial radiotherapy.

**No focal cause** is identified and it is postulated that it may occur due to post irradiation **demyelination**.

**No specific therapy** is required, some case reports suggest that **corticosteroids** may be of use but the evidence is not firmly established.

### **Hepatic Veno-Occlusive Disease (VOD) = Sinusoidal obstruction syndrome**

It is a complication of high dose chemotherapy given before a bone marrow transplant (BMT).

The name Sinusoidal obstruction syndrome is preferable if VOD happens as a result of chemotherapy or BMT.

It usually occurs within 2 weeks of BMT.

Features: weight gain, fluid retention, ascites, impending pulmonary oedema, pleural effusion, hepatomegaly, Jaundice with elevated liver enzymes, complicated by MOF.

Diagnosis: Abd U/S, Liver biopsy shows centrilobular necrosis.

TTT: Supportive: fluid balance, heparin & tPA.

### **Monoclonal antibodies**

Monoclonal antibodies have an increasing role in medicine.

They are manufactured by a technique called somatic cell hybridization.

This involves the fusion of myeloma cells with spleen cells from a mouse that has been immunized with the desired antigen. The resulting fused cells are termed a **hybridoma** and act as a 'factory' for producing monoclonal antibodies.

The main limitation to this is that mouse antibodies are immunogenic leading to the formation of human anti-mouse antibodies (HAMAs). This problem is overcome by combining the **variable region** from the **mouse** body with the **constant region** from **a human antibody**.

Clinical examples of monoclonal antibodies:

- **Infliximab (anti-TNF):** used in RA and Crohn's.
- **Rituximab (anti-CD20):** used in **RA** and **non-Hodgkin's lymphoma**.
- **Cetuximab (Epidermal growth factor receptor antagonist):** used in metastatic colorectal cancer and head and neck cancer.
- **Abciximab (glycoprotein IIb/IIIa receptor antagonist):** prevention of ischaemic events in patients undergoing PCI.
- **Trastuzumab (Herceptin) (HER2/neu receptor antagonist):** used in metastatic breast cancer. >> side effect: **Cardiotoxicity (DCM)** more common when **anthracyclines** have also been used.>> so an **echo** is usually performed **before** starting treatment
- **Alemtuzumab (anti-CD52):** used in **chronic lymphocytic leukaemia**.
- **OKT3 (anti-CD3):** used to prevent organ rejection

Monoclonal antibodies are also used for:

- Medical imaging when combined with a radioisotope.
- Identification of cell surface markers in biopsied tissue.
- Diagnosis of viral infections.

### **Interferons (IFN)**

Interferons (IFN) are cytokines released by the body in response to viral infections and neoplasia.

They are classified according to cellular origin and the type of receptor they bind to.

IFN-alpha and IFN-beta bind to type 1 receptors whilst IFN-gamma binds only to type 2 receptors.

**IFN-alpha** is produced by leucocytes and has an antiviral action. It has been shown to be useful in the management of:

- **Hepatitis B & C,**
- **Kaposi's sarcoma,**
- **Metastatic renal cell cancer,**
- **Polycythaemia rubra vera,**
- **CML**
- **Hairy cell leukaemia.**

Side effects of IFN-alpha:

- Flu like symptoms
- Depression
- Neutropenia → immunosuppression
- Erythema, pain, hardness on the spot of injection

### **Spinal cord compression**

Spinal cord compression is an oncological emergency and affects up to 5% of cancer patients.

Extradural compression accounts for the majority of cases, usually due to vertebral body metastases. It is more common in patients with lung, breast and prostate cancer.

Features:

- 1) **Back pain** - the earliest and most common symptom - may be worse on lying down and coughing.
- 2) Lower limb weakness.
- 3) Sensory changes: sensory loss and numbness
- 4) Neurological signs depend on the level of the lesion:
  - Lesions above L1 usually result in UMN signs in the legs and a sensory level.
  - Lesions below L1 usually cause LMN signs in the legs and perianal numbness. Tendon reflexes tend to be increased below the level of the lesion and absent at the level of the lesion.

Management:

- 1) **High-dose oral dexamethasone.**
- 2) Urgent oncological assessment by **urgent MRI** for consideration of radiotherapy or surgery.

Suspected Spinal cord compression >>> Oral dexamethasone + Urgent MRI
---

Metastatic bone pain >>> may respond to <b>NSAIDs, bisphosphonates</b> or <b>radiotherapy</b>
---

### **Gingival hyperplasia**

Drug causes of gingival hyperplasia:

- **Phenytoin**
- **Cyclosporine**
- **CCB** (especially Nifedipine)

Other causes of gingival hyperplasia include:

- **AML** (Acute myeloid leukaemia) (myelomonocytic and monocytic types)

### **Hormone replacement therapy (HRT): adverse effects**

HRT involves the use of a small dose of oestrogen (**combined with a progestogen in women with a uterus**) to help alleviate menopausal symptoms.

Side-effects:

- 1) Nausea
- 2) Breast tenderness
- 3) Fluid retention and weight gain

Potential complications:

- 1) Increased risk of **breast cancer**: increased by the addition of a progestogen.
- 2) Increased risk of **endometrial cancer**: reduced by the addition of a progestogen but not eliminated completely. The BNF states that the additional risk is eliminated if a progestogen is given continuously.
- 3) Increased risk of **venous thromboembolism**: increased by the addition of a progestogen.
- 4) Increased risk of **cerebrovascular stroke**. (BNF states that the stroke risk is the same regardless of whether the HRT preparation contains progesterone or oestrogen only).
- 5) Increased risk of **ischaemic heart disease** if taken more than 10 years after menopause.

Breast cancer:

- In the Women's Health Initiative (WHI) study there was a relative risk of 1.26 at 5 years of developing breast cancer
- The increased risk relates to duration of use



- The breast cancer incidence is higher in women using combined preparations compared to oestrogen-only preparations
- The risk of breast cancer begins to decline when HRT is stopped and by 5 years it reaches the same level as in women who have never taken HRT.
- **This is the rationale behind giving women who've had a hysterectomy oestrogen-only treatment.**

**EX:** Old woman who has **had a hysterectomy** presents for advice about **HRT**. Which one of the following would result from the use of a **combined** oestrogen-progestogen preparation compared to an oestrogen-only preparation >> ↑ **Increased risk of breast cancer.**

### **Blood product transfusion complications**

Complications:

- **Haemolytic:** immediate or delayed
- **Non-haemolytic** febrile reactions
- Transmission of viruses, bacteria, parasites
- Hyperkalaemia
- Iron overload
- ARDS
- Clotting abnormalities

Immediate haemolytic reaction:

- e.g. ABO mismatch
- Massive intravascular haemolysis

Febrile reactions:

- Due to white blood cell HLA antibodies
- Often the result of sensitization by previous pregnancies or transfusions
- It has a benign course.
- It is important to differentiate it from the haemolytic reaction
- TTT: stop transfusion + Paracetamol

Causes a degree of immunosuppression

- e.g. patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

The common viral infections considered in the infective risks of a blood transfusion are hepatitis B, hepatitis C and HIV.

The risks are variable depending on the source of donation and the type of testing employed.

In the United Kingdom:

أقل حاجة فى انجلترا واحد فى المليون

-The risks for **hepatitis B** are in the order of **1 per 1.3 million** donations while

-For **HIV** are **1 in 6.5 million** donations

-**Hepatitis C** and **1 in 28 million** donations.

A broad knowledge of the risks may be required while consenting a patient for blood transfusion.

N.B: Which type of infection is most likely to occur following a **platelet transfusion**?  
>> **Bacterial contamination.**

As platelet concentrates are generally stored at room temperature 22 °C, they provide a more favourable environment for bacterial contamination than other blood products.

In contrast packed red cells are stored at an average of 4°C while fresh frozen plasma as well as cryoprecipitate are stored at -30°C.

Factor VIII concentrates are heat inactivated freeze dried products with a minimal risk of bacterial contamination.

### **Delayed haemolytic transfusion reaction:**

It occurs **24 hours after** the transfusion.

Also it can be occur up to **5-10 days after** transfusion.

It is due to the development of red cells

This happens in a patient who **has been previously immunised** by transfusions or pregnancy.

The antibodies are not detectable initially but become obvious as a secondary immune response to the antigen exposure during the transfusion occurs.

Clinical features are usually **minimal** but can include **unexplained drop of Hb**, **unexplained pyrexia**, **jaundice** and **dark urine** after few days of transfusion.

The following should be carried out:

- 1) Hb level
- 2) Blood film: fragile ballooned spherocytes.
- 3) LDH
- 4) Serum bilirubin
- 5) Haptoglobin
- 6) **Direct Coombs' test** = **Direct anti-globulin test (DAT)**:
  - It detects the presence of antibody on RBCs.
  - The test is performed by adding AHG (Antihuman globulin) (anti-IgG and anticomplement) to the patient's washed RBCs.
  - A positive test results in RBCs agglutination.
- 7) Renal profile
- 8) Urinalysis for haemoglobinuria.

The group and antibody screen should be repeated.

**EX:** A patient on a medical ward received a transfusion **48 hours ago** for symptomatic anaemia on a background of CKD and COPD.

He gives a history of previous transfusions in the last year.

The patient has now dropped his Hb by 20 g/L compared to his pre-transfusion level and reports a dark coloured urine.

The LDH and bilirubin are elevated.

The most likely to this is >>> **Delayed haemolytic transfusion reaction:**

DD: Transfusion-associated graft versus host disease (GVHD), and

DD: Acute hepatitis as an infective complication both would be expected to occur in a one or two weeks.

DD: Acute haemolysis which would be expected to occur during the transfusion.

**EX:** A 75-year-old woman receives 2 units of packed red cells following a hip replacement. One week later her Hb concentration had fallen by 4 g/L.

The most likely to indicate a **delayed immune haemolytic transfusion reaction** is >>> **Positive direct anti-globulin test (DAT) being diagnostic.**

**EX:** Patient follow up **post-operative by 5 days** which he has received 2 units Packed RBCS, now he has drop of Hb 7, jaundice, dark urine >>>? **Delayed transfusion reaction** >>> Diagnosis by: **Direct Coombs' test**

**Transfusion related acute lung injury (TRALI)** occurs in patients **who have received** a multi-unit blood transfusion **previously** and are then re-transfused some time later e.g. in multiparous, she can develop **ARDS/ non cardiogenic pulmonary oedema** within 6 hours of blood transfusion.

Non cardiogenic pulmonary oedema can be differentiated from fluid overload by measurement of BNP.

It is diagnosed clinically and is thought to be significantly underdiagnosed.

It is thought to be related to **anti-HLA** or **anti-granulocyte antibodies** in the **donor** blood.

Despite the fact that the donor and recipient are matched, the possibility of anti-granulocyte antibodies cannot be excluded.

Two hypotheses are proposed for the cause of TRALI that it is either

- Due to **HLA antigens in the donor blood** reacting with neutrophil antigens in the patient, leading to neutrophil migration to pulmonary capillaries

Or that

- The neutrophils responsible do not actually require donor HLA antigens to react, and are just primed by infection, surgery or inflammation.

What is common to both hypotheses though, is that the neutrophils lead to a local release of cytokines, increased capillary permeability, and **non-cardiogenic pulmonary oedema**, accounting for the presentation with wheeze and hypoxia.

Diagnosis can be confirmed by the finding of **anti-HLA** or **antineutrophil antibodies** in the **donor** or **recipient**.

Mortality is at between 5-15% depending on case series.

TTT:

- Mainly by **full respiratory support** as the condition is reversible after few days, with possible transfer to **ICU** for consideration of intubation & Ventilation if required.
- **Donors** who carry such antibodies are **resigned** from the donor pool.
- When **recipients** who have developed TRALI require further transfusion, **male donor** can be used to reduce the risk of subsequent attacks, this is because they have a much lower rate of carriage of anti-HLA or antineutrophil antibodies (1-5% vs up to 20% in women).

**The most common indications for irradiated blood products include:**

Those at risk of transfusion associated with graft versus host disease (**GVHD**) (it prevent viable T lymphocytes in the donation engrafting and causing transfusion-associated GVHD). Such cases as:

- 1) Neonates
- 2) Hodgkin's lymphoma.
- 3) Those receiving purine analogues based chemotherapy.
- 4) Immunodeficiency states.
- 5) Post bone marrow transplantation.

**Gamma Irradiation** of blood does not affect its quality.

Patients should be informed that they need irradiated blood products and given an information card.

CMV is a transfusion-transmitted infection that can be fatal in stem cell transplant recipients, so it is good practice to use CMV negative products.

**Post bone marrow transplant** with anaemia and in need PRBCs blood transfusion or with sever thrombocytopenia and in need for platelet transfusion >>> **Gamma Irradiated** مشعشع & **CMV-negative** red cells or PLT.

**Post bone marrow transplant acute graft versus host disease (GVHD):**

This presents **within 100 days** of bone marrow transplantation.

But, chronic GVHD occurring 100-300 days post-transplant.

Presented with a **triad** of **skin rash** (can progress to Erythroderma), **liver dysfunction** (cholestatic jaundice) and **Diarrhea** (sometimes bloody).

GVHD is graded according to the Seattle system, and each organ involved is scored (**skin, liver and gut**).

It remains a **serious** cause of mortality and morbidity amongst BM TX Rx.

TTT: **Pulse methylprednisolone IVI** + TPN ± tPA and prostacyclin only if associated with veno-occlusive disease.

Also add immunosuppresses as **cyclosporine**, Tacrolimus and MMF.

**EX:** A 33-year-old male develops a rash and low grade fever (37.6°C) 20 days post allogeneic bone marrow transplant for high risk AML in first complete remission. The rash is initially maculopapular affecting palms and soles but 24 hours later general Erythroderma is noted affecting the trunk and limbs. His total bilirubin was previously normal but is now noted to be 40 µmol/L (1-22). He remains very well in himself >>> **Acute GVHD >>> TTT Pulse methylprednisolone IVI.**

**The storage conditions and shelf life of blood products:**

-Red cells are stored at 4°C for up to 35 days and يوم 30

-Platelets at 22°C for 5 days on a platelet shaker/agitator.

-Fresh frozen plasma can be stored up to 24 months at -30°C. شهر 30

The **minimum dataset** for identifying a patient and a sample for purpose of a non-emergency blood transfusion: **Full name**, **DOB** and **patient ID**.

Address (in some areas, such as Wales),

Previous blood grouping details are not required

The **most common error** in transfusion according to the **SHOT** (serious hazards of transfusion) analysis is >>> **Wrong identification or mislabelling of patient or sample or requests.**

Other errors such as cross match error, incorrect storage and transfusion reaction due to an antibody not detected do occur but are rare.

A '**group and save**' is adequate for **elective** surgeries and is standard practice in most modern blood banks. This will involve blood grouping and its confirmation as well as an antibody screen.

Other options include cross match and a direct Coombs' test (Direct anti-globulin test or DAT) which are often done only if the antibody screen test is positive. These are

not routinely done for elective surgery unless the patient has had a recent blood transfusion or a history of previous known red cell antibodies.

In a stable patient **red cell packs (PRBCs)** may be transfused **over 90-120 minutes** while a **platelet** transfusion should **not take more than 20-30 minutes**.

Rapid infusion of PRBCs or FFP may be required in acutely bleeding patient but not in this patient who is stable.

#### **Manufacture of pooled plasma derivatives:**

-The plasma derivatives (such as factor VIII) are prepared **from several thousand plasma donations**, typically 20,000, or 5,000 kg of plasma at a time.

-**Pooled plasma** has been sourced from outside UK since **1999** to avoid **vCJD** risks.

-The process **involves several chemical steps** including ethanol extraction, chromatography and **viral inactivation steps** which results in a freeze dried product.

-These products have a **long shelf life of several months to years**.

The **blood** to be used for an **exchange transfusion** in a **neonate** should fulfil the following criteria: plasma reduced whole blood in CPD (citrate phosphate dextrose/anticoagulant), irradiated and less than 5-days-old.

The **Rh** group should be **compatible with the mother, not the neonate**, to avoid haemolytic transfusion reaction in the neonate due to maternal Rh antibodies.

**EX:** A 45-year-old woman being treated for acute myeloid leukaemia (AML) fails to get sufficient rises with platelet transfusions. She is 14 days post chemotherapy, afebrile and apart from minor bruising is otherwise well.

The next best step in the management of **platelet refractoriness** >>> **Check for a one hour post platelet transfusion platelet count**.

Patients who are **refractory to platelet transfusions** should **first** be investigated to **check for adequate platelet rises**. This is best done **on a one or two hour post platelet transfusion sample**.

Further management would include checking for **HLA antibodies** but requesting HLA matched platelets at this stage would not be appropriate.

Continuing random platelet transfusions or requesting a directed platelet donation are also not appropriate at this stage.

Platelets are obviously indicated in this patient until recovery of blood counts and hence cannot be avoided.

- **Blood Group O:** The red cells have absent A/B antigen and plasma has anti A and anti B antibodies.
- **Blood Group AB:** The red cells have A /B antigen but no antibodies in the plasma.
- **Blood Group A:** The red cells have antigen A and plasma has anti B antibodies.
- **Blood Group B:** The red cells have antigen B and plasma has A antibodies.

Approximately **1% of pregnant women** develop clinically important red cell antibodies, the most common being **rhesus antibodies**.

The women negative for D antigen develop antibodies on exposure to D positive blood (such as fetomaternal haemorrhage (FMH), abortions and transfusions).

This increases the risk of haemolytic disease of the Newborns (**HDN**) in **subsequent** pregnancies.

**Following delivery**, the **degree of fetomaternal haemorrhage (FMH)** should be **calculated on a blood sample from a D negative mother** to adjust the dose of anti D in the D negative mother delivering a D positive child.

D positive women and D negative women have the **same chances** of developing antibodies to other red cell antigens.

All pregnant women should have a **blood group and antibody screen** in their **first** trimester or at presentation, whichever is earlier.

The fetal Rh type depends on the paternal and maternal Rh typing.

Maternal antibody **titres correlate** with the degree of haemolytic disease of the newborn (HDN).

If a **female patient** has been given **Rh D positive platelets** when she is **RhD negative**, she is therefore by now (five days later) likely to have made **immune anti-D**.

It is very often necessary to give D positive platelets to D negative people due to platelet shortage.



If the recipient of this mismatch is a **female of child bearing age** then **prophylactic anti- D should be administered** with the platelets to prevent production of immune anti- D.

If she become pregnant in the future, the immune anti-D she has made can cross the placenta and **cause haemolytic disease of the fetus/newborn**, if the **baby is D positive**, and this can be life threatening to the baby.

Therefore any pregnancies would have to be managed by an obstetrician with special interest in fetal medicine and the baby closely monitored and the **levels of anti-D in the mother** monitored.

In **70%** of testicular tumours either **Beta-HCG** which is raised in seminomatous germ cell tumours or **AFP** which is raised in non-seminomatous germ cell tumours.

The incidence of testicular tumours is **2-3 cases / 100,000 men per year** and they account for **1-2% of all cancers in males**.

Average age at presentation is **20-44 years old**.

TTT: Orchiectomy ± Radiotherapy or chemotherapy.

Bleomycin is an antimitotic agent used for the ttt of testicular tumours and a serious SE is pulmonary fibrosis.

### **Testicular Seminoma:**

It is a germ cell tumour (**GCT**), testicular GCTs are **rare**.

They are the most common malignancy in men aged **15-35** years old.

The most common presentation is with a **painless testicular lump** that has been present for several days to months.

**Cryptorchidism** is associated with a greatly increased risk of seminoma (10-40 times), although surgery in many cases permits earlier detection of the tumour.

Around 75% of patients present with localised disease, 15% regional LN involvement, and around 10% with distant metastasis (e.g. to lungs).

**Scrotal US** is the investigation of **choice**: typically a **hypoechoic mass** with areas of **calcifications**.

**Beta-HCG** is the most specific tumour marker for Testicular Seminoma, however it is **only** elevated in 5-10% of cases, and the level of elevation correlates with **metastasis**.

Due to commonality between B-HCG and TSH, profound rise in B-HCG result in **hyperthyroidism** (↓↓ **TSH**) so symptoms of weight loss and anxiety.

Testicular biopsy is not recommended.

TTT: **Orchiectomy**.

### **Ewing's sarcoma:**

It is the **most lethal malignant primary** bone tumour derived from the red bone marrow.

It is most common in **children and adolescents** and rare after the age of 30 years.

It has a **male**: female ratio about 3:2.

The earliest symptom is **pain**, which is usually **intermittent** but becomes increasingly intense.

Delay in the diagnosis can occur due to the fact that the clinical picture may **be similar to that of acute or chronic osteomyelitis**. However, eventually most patients have a **large palpable rapidly growing mass**, which is tense and tender.

Associations with a poor prognosis include the **male** sex, **age > 12 years**, ↑ **elevated LDH**, **anaemia** and a poor response to chemotherapy.

### **Extravasation of the chemotherapeutic agents:**

- **Stop the infusion, immobilize** the arm and attempt to **aspirate** any accessible drug from the cannula and extravasation site before removal of the cannula.
- Agent specific **antidote** can be used after specialist advice.
- **Cold compresses** are generally applied except in the case of **vinca alkaloids** in which case a **heat** compress should be applied.
- Doxorubicin and Daunorubicin extravasation injuries are particularly prone to causing ulceration and so **plastic surgery** opinion is needed.
- Consider **reporting** to National Extravasation Information Service.

### Palliative care prescribing: pain

#### NICE guidelines:

In 2012 NICE published guidelines on the use of opioids in palliative care.

#### Starting treatment:

- When starting treatment, offer patients with advanced and progressive disease regular oral modified-release (MR) or oral immediate-release morphine (depending on patient preference), with oral immediate-release morphine for breakthrough pain.
- If no comorbidities use 20-30mg of MR a day with 5mg morphine for breakthrough pain. For example, 15mg modified-release morphine tablets twice a day with 5mg of oral morphine solution as required.
- Oral modified-release morphine should be used in preference to transdermal patches.
- Laxatives should be prescribed for all patients initiating strong opioids.
- Patients should be advised that nausea is often transient. If it persists then an antiemetic should be offered.

#### SIGN guidelines:

SIGN issued guidance on the control of pain in adults with cancer in 2008.

- The breakthrough dose of morphine is one-sixth the daily dose of morphine.
- All patients who receive opioids should be prescribed a laxative.
- Opioids should be used with caution in patients with chronic kidney disease. Alfentanil, buprenorphine and fentanyl are the preferred opioids in CKD.
- Metastatic bone pain may respond to NSAIDs, bisphosphonates or radiotherapy.

#### Other points:

When increasing the dose of opioids the next dose should be increased by 30-50%.

#### Opioid side-effects:

Usually transient	Usually persistent
Nausea Drowsiness	Constipation

**Conversion between opioids:**

From	To	Conversion factor
Oral codeine	Oral morphine	Divide by 10
Oral tramadol	Oral morphine	Divide by 10*

Oxycodone generally causes less sedation, vomiting and pruritis than morphine but more constipation.

From	To	Conversion factor
Oral morphine	Oral oxycodone	Divide by 1.5-2**

The current BNF gives the following conversion factors for transdermal preparations:

- A transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily.
- A transdermal buprenorphine 10 microgram patch equates to approximately 24 mg oral morphine daily.

From	To	Conversion factor
Oral morphine	Subcutaneous diamorphine	Divide by 3
Oral oxycodone	Subcutaneous diamorphine	Divide by 1.5

\*This has previously been stated as 5 but the current version of the BNF states a conversion of 10

\*\*Historically a conversion factor of 2 has been used (i.e. oral oxycodone is twice as strong as oral morphine). The current BNF however uses a conversion rate of 1.5

Morphine acts for 4 to 5 hours while pethidine works for 2 to 3 hours.

This means that **pethidine** would have to be given at **more frequent intervals** to produce the same analgesic effects as morphine.

**Morphine** is **effective for the treatment of most types of pain** especially when given in combination with NSAIDs for bone pain or gabapentin for neuropathic pain.

Morphine is extensively metabolised in the liver to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).

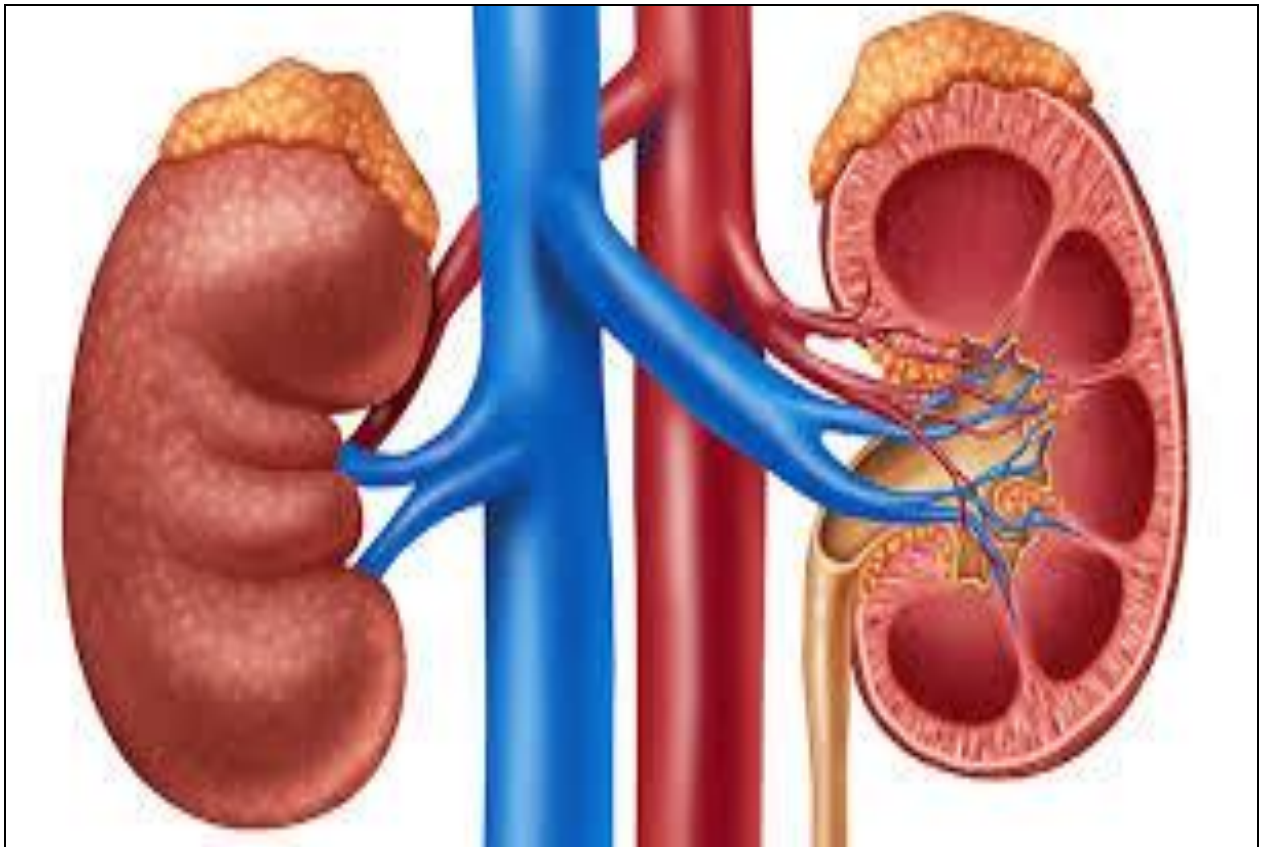
M6G appears to have analgesic effects and it is 2 to 4 times more potent than morphine. **M6G** is primarily **excreted by the kidneys**, thus accumulation occurs in renal failure and is likely to cause **opioid toxicity**.

**Fentanyl** is a **synthetic opioid** extensively metabolised by cytochrome P450 enzymes in the **liver** and gastrointestinal tract, thus **it is unaffected by renal impairment**. Due to its extensive first pass metabolism, it can only be given parenterally (that is, transmucosal, transdermal, IM, IV or SC).

**So Fentanyl injection is safe in cases of renal impairment.**

Transdermal fentanyl alone has no place for the treatment of acute pain; as steady state will only be obtained more than 24 hours post-application.

# Nephrology



**Acute renal failure: Prerenal uraemia vs. Acute Tubular Necrosis (ATN)**

Prerenal uraemia >>>> kidneys hold on to sodium to preserve volume.

	Pre-renal uraemia	Acute tubular necrosis (ATN)
Urine sodium	< 20 mmol/L	> 40 mmol/L
Fractional sodium excretion*	< 1%	> 1%
Fractional urea excretion**	< 35%	>35%
Urine osmolality	>500	<350
Urine: plasma osmolality	> 1.5	< 1.1
Urine: plasma urea	> 10:1	< 8:1
Specific gravity	> 1020	< 1010
Urine	'bland' sediment	brown granular casts (NOT RBCS cast)
Response to fluid challenge	Yes	No

\*Fractional sodium excretion = (urine sodium/plasma sodium) / (urine creatinine/plasma creatinine) x 100.

\*\*Fractional urea excretion = (urine urea /blood urea) / (urine creatinine/plasma creatinine) x 100.

Normal plasma osmolality = 278 – 305 mOsmol/Kg

Normal urinary osmolality = 350 – 1000 mOsmol/Kg

Of the acute renal failure seen by physicians 80-90% will fall into the category of pre-renal failure or ATN.

The urinary abnormalities in **ATN** suggest **tubular dysfunction** (that is, urinary sodium greater than 40 mmol/L, low urinary osmolality less than 350 mOsmol/L).

**Red cell casts present in:**

- **Acute glomerulonephritis**
- **Renal vasculitis**
- Accelerated **hypertension** and
- **Interstitial nephritis.**

Oliguria is defined as <400 ml urine/day.

Causes of ARF can be divided into pre-renal, renal and post-renal.

- **Pre-renal:**
  - Hypovolaemia (GE, burns, sepsis, Hge, nephrotic syndrome).
  - Circulatory failure.
- **Renal:**
  - **Glomerular:** GN
  - **Tubular:** ATN, ischaemic, toxic, obstructive
  - **Interstitial:** interstitial nephritis, pyelonephritis
  - **Vascular:** renal vein thrombosis, embolus, HUS, vasculitis.
  - Acute on top of chronic renal failure.
- **Post-renal:**
  - Obstruction, either congenital or acquired.

**ADPKD (Autosomal dominant polycystic kidney disease)**

- **Autosomal dominant** polycystic kidney disease (**ADPKD**) is the most common inherited cause of kidney disease, affecting 1 in 1,000 Caucasians.
- **So offspring** of a parent with the disease have a **50% chance** of having the condition.
- The symptoms do **not** tend to **occur before the age of 40**.
- It is responsible for around 10% of the UK dialysis burden.
- Approximately **half** of patients with ADPKD will reach **ESRD** by the age of **60** and require renal replacement therapy.
- It is due to a mutation in the **PKD1 gene**.
- The PKD1 gene encodes for a **polycystin-1**, a large cell-surface glycoprotein of unknown function.
- Two disease loci have been identified, PKD1 and PKD2, which code for polycystin-1 and polycystin-2 respectively.
- **Genetic counselling** should be offered
- Regular follow up in renal clinic every 6 months



➤ TTT:

- **ACEI** is the therapy of choice with Regular follow up of BP and renal function.
- High fluid intake (to prevent the formation of renal stones or blood clots).
- Loin pain should be treated symptomatically, and
- Haematuria should be treated conservatively.
- UTIs should be treated with lipophilic drugs (for example, ciprofloxacin, TMP\_SM) as they have the best penetration into cyst fluid.

ADPKD type 1	ADPKD type 2
<b>85%</b> of cases	15% of cases
Chromosome <b>16</b>	Chromosome <b>4</b>
Presents with renal failure earlier	

ADPKD type 1 = chromosome 16 = 85% of cases

The screening investigation for relatives is **abdominal ultrasound**.

**Ultrasound diagnostic criteria (in patients with positive family history):**

- Two cysts, unilateral or bilateral, if aged < 30 years
- Two cysts in both kidneys if aged 30-59 years
- Four cysts in both kidneys if aged > 60 years

CT is more sensitive than USS and may aid in diagnosis in younger patients.

MRA angiography: In patients with a family history of intracranial aneurysm - to screen for cerebral aneurysms.

Screening is recommended after 20 years age (if < 20 yrs. age >>>> Ultrasound gives false -ve result and CT is *not* needed as it will involve unnecessary high radiation dose to this young boy or girl, so just follow up US at the age of 20 years old age).

Cysts usually develop during teenage years, so one cannot be confident a child has not been affected until they are at least 20 years.

A normal ultrasound scan at 20 years of age means you can be 90% confident they are not affected, a normal scan at 30 years increases the confidence level to 98%.

Formal **screening for AKPD** occurs in early adulthood, usually with a renal **ultrasound** scan. Its sensitivity approaches **100% in those over 30 years**, but falls to less than 70% under this age.

For the diagnosis to be made there should be **at least two cysts in one or both kidneys**.

ADPKD is like a **CKD** with **high phosphate, low calcium** but with normal/high Hb due to excess erythropoietin secretion.

**Associated conditions:**

- **Hypertension** (in over **75%** of cases).
- **Colonic diverticulae** >>>>> screen by barium enema.
- Mitral valve prolapse (**MVP**) in **25%** and **AR** >>>> screen by echo.
- **Cerebral berry aneurysms** in 25% >>> **SAH** >>> **MRA** or CT angiography.
- Excessive **erythropoietin** production and polycythaemia.
- **Hepatic cysts** in **80%**, also involve the **pancreas** (10%), **ovaries** (amenorrhea) and spleen.
- **Renal cell carcinoma with lung metastasis**: it is very rare but recognized complication of ADPKD >>> **CT Thorax & Abdomen**.

**NB:** Current consensus is that screening for cerebral aneurysms should **only** be carried out in **high risk patients**. These include factors such as:

- 1) Previous rupture of aneurysm
- 2) Concerning neurological symptoms (for example, severe headache)
- 3) Positive family history of haemorrhagic stroke or aneurysm.

Even if aneurysms are found, the rupture risk can still be low and the morbidity implications of curative surgery may outweigh conservative management.

### **ARPKD**

Autosomal recessive polycystic kidney disease (ARPKD) is much less common than autosomal dominant disease (ADPKD). It is due to a defect in a gene located on chromosome 6.

**The autosomal recessive form is rare and usually causes death in childhood.**

Diagnosis may be made on prenatal ultrasound or in early infancy with abdominal masses and renal failure. Newborns may also have features consistent with Potter's syndrome secondary to oligohydramnios. End-stage renal failure develops in childhood. Patients also typically have liver involvement, for example portal and interlobular fibrosis.

Renal biopsy typically shows multiple cylindrical lesions at right angles to the cortical surface.

### **Alport's syndrome**

It is usually inherited in an X-linked dominant (XLD) pattern\*.

Prevalence is **around 1 in 5000**, It is due to a defect in the gene which codes for type **IV** (4) collagen resulting in an abnormal glomerular-basement membrane (**GBM**).

The disease is more severe in males with females rarely developing renal failure.

**Deafness** usually occurs **before** the onset of renal failure, which is related itself to progressive nephritis.

Rigorous control of **hypertension** may delay the onset of **ESRD**, which is seen in **90% of patients with Alport's by the age of 40 years.** ☹

<b>90% of Alport's syndrome develop renal failure by the age of 40 years.</b>
---

A favourite question is an Alport's patient with a failing renal transplant. This may be caused by the presence of anti-GBM antibodies **leading to a Goodpasture's syndrome like picture.**

Alport's syndrome usually presents in childhood. The following **5** features may be seen:

- 1) **Microscopic haematuria.**
- 2) **Progressive renal failure.**
- 3) **Bilateral sensorineural deafness.**

- 4) **Ocular** abnormalities: **Lenticonus** (protrusion of the lens surface into the anterior chamber), **Corneal ulceration**, Corneal dystrophy, **Cataract**, **Retinitis pigmentosa**.
- 5) Renal biopsy: **splitting of lamina densa seen on electron microscopy**, light microscopy may be unremarkable.

\*In around 85% of cases - 10-15% of cases are inherited in an autosomal recessive fashion with rare autosomal dominant variants existing

Alport's syndrome - X-linked dominant (**XLD**) (in the majority)

Alport's syndrome - type **IV** 4 collagen defect

### Chronic kidney disease: causes

Common causes of chronic kidney disease:

- 1) Diabetic nephropathy
- 2) Chronic glomerulonephritis
- 3) Chronic pyelonephritis
- 4) Hypertension
- 5) Adult polycystic kidney disease

CKD on haemodialysis - most likely cause of death is **IHD**

Cardiovascular events account for 50% of the mortality in patients receiving dialysis.

### Chronic kidney disease: eGFR and classification

Serum Creatinine may not provide an accurate estimate of renal function due to differences in muscle.

For this reason formulas were developed to help estimate the glomerular filtration rate (estimated GFR or eGFR).

The most commonly used formula is the Modification of Diet in Renal Disease (MDRD) equation, which uses the following variables:

- 1) Serum **Creatinine**
- 2) **Age**
- 3) **Gender**
- 4) **Ethnicity**

GFR variables - **CAGE** - Creatinine, Age, Gender, Ethnicity

Factors which may affect (invalidate) the result:

- Pregnancy
- Muscle mass (e.g. amputees, body-builders)
- Eating red meat 12 hours prior to the sample being taken

The NICE guidelines on the identification and management of CKD recommend that **screening for CKD** should be offered to patients with:

- 1) DM
- 2) Hypertension
- 3) Cardiovascular disease
- 4) Structural renal tract pathology
- 5) Multisystem disease with potential renal involvement
- 6) Opportunistically detected haematuria or proteinuria
- 7) A family history of stage 5 CKD, or
- 8) Hereditary kidney disease.

The guidelines recommend that age, gender, obesity and ethnicity should **not** be used as risk markers to test people

**CKD may be classified according to GFR:**

CKD stage	GFR range
<b>1</b>	Greater than 90 ml/min, with some sign of kidney damage on other tests. <b>(if all the kidney tests* are normal, so&gt;&gt;&gt;&gt; there is no CKD)</b>
<b>2</b>	60-90 ml/min with some sign of kidney damage (if kidney tests* are normal, there is no CKD).
<b>3a</b>	45-59 ml/min, a moderate reduction in kidney function.
<b>3b</b>	30-44 ml/min, a moderate reduction in kidney function.
<b>4</b>	15-29 ml/min, a severe reduction in kidney function.
<b>5</b>	<b>Less than 15 ml/min</b> , established kidney failure - dialysis or a kidney transplant may be needed.

\*i.e. Normal U&Es and no proteinuria.

**NB:**

CKD: only diagnose stages 1 & 2 >>> if supporting evidence to accompany eGFR

- Chronic kidney disease especially stages I & II is only diagnosed if supporting tests such as urinalysis or renal ultrasound are abnormal with the reduced GFR (i.e. not only with reduced eGFR accompanied with normal urinalysis or renal ultrasound).
- (Ex. Pt. with eGFR 60 ml/min and normal U&E, urine analysis and Abd u/s >>>> so no CKD)
- The eGFR is often inaccurate in people with extremes of muscle mass. Body builders often have an inappropriately low eGFR.

**Chronic kidney disease: hypertension**

The majority of patients with CKD will require more than 2 drugs to treat HTN.

**ACE inhibitors:**

- They are first line and are particularly helpful in proteinuric renal disease (e.g. diabetic nephropathy).
- As these drugs tend to reduce filtration pressure a small fall in glomerular filtration pressure (GFR) and rise in creatinine can be expected.
- NICE suggest that a decrease in eGFR of up to 25% or a rise in creatinine of up to 30% is acceptable, although any rise should prompt careful monitoring and exclusion of other causes (e.g. NSAIDs). A rise greater than this may indicate underlying renovascular disease.

**Furosemide:**

- It is useful as an anti-hypertensive in patients with CKD, particularly when the GFR falls to below 45 ml/min\*.
- It has the added benefit of lowering serum potassium.
- High doses are usually required.
- If the patient becomes at risk of dehydration (e.g. Gastroenteritis) then consideration should be given to temporarily stopping the drug.

\*The NKF K/DOQI guidelines suggest a lower cut-off of less than 30 ml/min.

The NICE guidelines on the management of CKD (CG182) recommend that patients with **CKD who have proteinuria** equivalent to **ACR ≥70 mg/mmol** should have their **BP controlled to the target range 120-129/<80 mmHg**. The **same** target range should be used in patients with **diabetes**.

The NICE guidelines recommend that a BP target range of 120-139/<90 mmHg should be used in **non-diabetic patients** with CKD and an ACR <70 mg/mmol.

Aiming for lower systolic (<120 mmHg) or diastolic (<60 mmHg) blood pressures increases the risk of mortality, cardiovascular disease, congestive cardiac failure and, in the case of low diastolic values, progression of chronic kidney disease.

Systolic or diastolic blood pressures above the target ranges are associated with increased risk of a doubling in serum creatinine, ESRF and death.

### Chronic kidney disease: proteinuria

- Proteinuria is an important marker of CKD, especially for diabetic nephropathy.
- NICE recommend using the albumin: creatinine ratio (**ACR**) in preference to the protein: creatinine ratio (PCR) when identifying patients with proteinuria as it has greater sensitivity.
- For quantification and monitoring of proteinuria, PCR can be used as an alternative, although ACR is recommended in diabetics.
- Urine reagent strips are not recommended unless they express the result as an ACR.

#### Approximate equivalent values:

ACR (mg/mmol)	PCR (mg/mmol)	Urinary protein excretion (g/24 h)
<b>30</b>	<u>50</u>	<u>0.5</u>
<b>70</b>	<u>100</u>	<u>1</u>

Average individuals pass around 10mmol urinary creatinine each day. Therefore:

- U PCR **50** = **500mg** protein/day
- U PCR **100** = **1000mg** protein/day

So, a 24 hour urinary protein collection of **1g** is therefore approximately equivalent to **urinary PCR of 100 mg/mmol**.

#### Collecting an ACR sample:

- By collecting a 'spot' sample it avoids the need to collect urine over a 24 hour period in order to detect or quantify proteinuria.
- Should be a first-pass morning urine specimen.
- If the initial ACR is greater than **30** mg/mmol and less than **70** mg/mmol, **confirm** by a subsequent early morning sample.
- If the initial ACR is greater than **70** mg/mmol a repeat sample need **not** be tested.

Interpreting the ACR results:

- In **non-diabetics** an ACR greater than **30** mg/mmol is considered clinically significant proteinuria.
- In **diabetics** microalbuminuria (ACR greater than **2.5** mg/mmol in men and ACR greater than **3.5** mg/mmol in women) is considered clinically significant.

**NB: Newly detected microalbuminuria in IDDM Pt. >>>> should be confirmed by repeat test 3-6 months period before starting ttt with ACEI/ARBs.**

### **Chronic kidney disease: bone disease**

Basic problems in chronic kidney disease:

- 1) **Low vitamin D** (1-alpha hydroxylation normally occurs in the kidneys).
- 2) **High phosphate:** due to **decreased renal excretion**.
- 3) **Low calcium:** due to lack of vitamin D, high phosphate.
- 4) **Secondary hyperparathyroidism:** due to low calcium, high phosphate and low vitamin D.

Several clinical manifestations may result:

- 1) **Osteitis fibrosa cystica:** >> aka hyperparathyroid bone disease
- 2) **Adynamic bone disease:**
  - a. reduction in cellular activity (both osteoblasts and osteoclasts) in bone
  - b. may be due to over treatment with vitamin D
- 3) **Osteomalacia:** due to low vitamin D
- 4) Osteoporosis
- 5) Osteosclerosis

The healthy adult kidney excretes **5400 mg per week** of phosphate.

**Dialysis** is able to remove **only** about **half** of the phosphate that the healthy kidney would be able to do.

So the maximum amount of phosphate that can be removed by dialysis in a patient with anuric renal failure who is dialysis dependent is **2700 mg / week**.



## Erythropoietin (EPO)

- Erythropoietin is a haematopoietic growth factor that stimulates the production of erythrocytes.
- The main uses of erythropoietin are to treat the anaemia associated with chronic kidney disease and that associated with cytotoxic therapy.
- Erythropoietin treats CKD associated anaemia which in turn would improve exercise tolerance. It does not improve renal function.

Side-effects of erythropoietin:

- 1) **Hypertension** - **20%** of patients require increased antihypertensive medications. It may even **precipitate a hypertensive crisis**. It should be avoided until BP is better controlled below 170/110 mmHg.
- 2) **Encephalopathy** and **seizures** (**EPO-induced epilepsy**): it is **rare** adverse event and can be seen **within 90 days** of EPO initiation.
- 3) **Hyperkalaemia**
- 4) Bone aches
- 5) Flu-like symptoms
- 6) **Anaphylaxis**: skin rashes, urticaria
- 7) **Pure red cell aplasia**: is a rare unwanted effect due to stimulation of antibodies by administered EPO which cross reacts with the patient's endogenous EPO, this risk is greatly reduced with darbepoetin.
- 8) Raised PCV increases risk of **thrombosis** (e.g. Fistula)
- 9) A dose-dependent **rise in platelet count** is common, due to erythropoietin affinity for thrombopoietin receptors.
- 10) Iron deficiency 2nd to increased erythropoiesis.

**NB:** Erythropoiesis-stimulating agents act as a growth factor in the context of **active malignancy**, and this increases the mortality of patients with malignancy (e.g. renal cell carcinoma) who receive erythropoietin. The other major risk factor associated with these drugs is **ischaemic stroke**.

There are a number of reasons why patients may fail to respond to erythropoietin therapy:

- 1) Iron deficiency
- 2) Inadequate dose
- 3) Concurrent infection/inflammation
- 4) Hyperparathyroid bone disease
- 5) Aluminium toxicity

**Before** initiation of recombinant erythropoiesis-stimulating agents the patient should be **iron replete by IV Iron** till **ferritin** is restored to mid-range > **100 µg/L** and **transferrin saturation >20%** with normal vitamin B12 and folate.

Oral iron is therapy usually ineffective, so **IV iron therapy** is required.

Blood transfusion should be avoided if possible as patient is fluid overloaded and it may precipitate pulmonary oedema.

Where possible blood transfusion should be avoided in patients who may be candidates for transplantation as the development of antibodies to alloantigen may make future transplantation more problematic.

The **serum ferritin** and **transferrin saturation** should be checked, as most patients will be iron deficient.

Targets for treatment for anaemia in CKD patients are:

- 1) **Haemoglobin 10-12 g/dl** (European renal guideline, target Hb **11 g/dl**).
- 2) **Ferritin: >100 µg/L** in pre-dialysis and peritoneal dialysis patients, **>200 µg/L** in haemodialysis patients
- 3) **Transferrin saturation >20%**

**Transferrin saturation (Fe/TIBC) : <20%** should be considered a marker of functional iron deficiency when the ferritin is >100 µg/L.

Where patients have absolute iron deficiency **oral** iron supplementation may be adequate. However where there is functional iron deficiency, **IV** iron replacement is recommended.

EPO abuse in **sports**: It can be detected in **urine** for a **few weeks** following the most recent injection.

### **Renal transplant: HLA typing and graft failure**

The human leucocyte antigen (**HLA**) system is the name given to the major histocompatibility complex (**MHC**) in humans.

It is coded for on chromosome **6**.

Some basic points on the HLA system:

- Class 1 antigens include A, B and C.
- Class 2 antigens include DP, DQ and DR.
- when HLA matching for a renal transplant the relative importance of the HLA antigens are as follows **DR > B > A**

Renal transplant HLA matching - **DR** is the most important

**Transplants** are classified as:

- 1) **Autografts**: in which the same individual acts as both donor and recipient.
- 2) **Isografts**: in which the donor and recipient are genetically identical (twins).
- 3) **Allografts**: where the donor and recipient are genetically dissimilar but belong to the same species (the commonest).
- 4) **Xenografts**: in which the donor and recipient belong to different species (between animal and human).

In **orthotopic** transplants: the transplanted part is placed in its normal anatomical location.

In **heterotopic** transplants: it is placed in different anatomical location.

**Graft survival:**

- For cadaveric transplants: 1 year = 90%, 10 years = 60%
- For living-donor transplants: 1 year = **95%**, 10 years = **70%**

**Post-op problems:**

- ATN of graft
- Vascular thrombosis
- Urine leakage
- UTI

**Hyperacute acute rejection (minutes to hours):**

- Due to **pre-existent antibodies** against donor HLA type 1 antigens (a type II hypersensitivity reaction) and is therefore **IgG** mediated.
- Rarely seen due to HLA matching.

**Acute graft failure (< 6 months):**

- Acute rejection develops in **30-50%** of renal transplant recipient, the risk is greater up to 2 weeks post-operatively.
- The risk is greater in the first 3 weeks after transplant.
- Usually due to mismatched HLA Cell-mediated (cytotoxic T cells).
- May be reversible with steroids and immunosuppressant.
- Other causes include:

- 1) Cytomegalovirus infection.
- 2) Cyclosporine toxicity (acute or chronic): drug-drug interaction especially with enzyme inhibitors like azithromycin.
- 3) ATN of the graft.
- 4) Vascular thrombosis.
- 5) Ureteric leakage from the anastomosis.

**Cytomegalovirus (CMV)** is the most common and important viral infection in solid organ transplant recipients >>> **Ganciclovir** is the treatment of choice.

**Chronic graft failure (> 6 months):**

- The pathogenesis of chronic rejection is not clear; some prefer the term "chronic allograft nephropathy" (CAN) since both immunological (antigen-dependent and antigen-independent) and non-immunological factors have been identified.
- Both antibody and cell mediated mechanisms cause fibrosis to the transplanted kidney (chronic allograft nephropathy) (CAN).
- Recurrence of original renal disease (MCGN > IgA > FSGS).
- Risk factors include:
  - Number of previous acute rejection episodes
  - Presence of anti-HLA antibodies
  - Anti-endothelial antibodies
  - CMV infection
  - Hypertension
  - Dyslipidaemia
  - Functional mass of the donor kidney, and
  - Delayed graft function (a clinical manifestation of ischaemia/reperfusion injury).

**Graft versus host disease (GVHD):**

GVHD occurs when **donor lymphocytes** engraft in a susceptible recipient.

Products implicated in cases of transfusion associated (TA)-GVHD include: ☹

- Non-irradiated whole blood
- Packed red blood cells
- Platelets
- Fresh non-frozen plasma.
- Granulocytes

The following have not been implicated: ☺

- Frozen deglycerolised red blood cells
- FFP and
- Cryoprecipitate.

In renal transplant there is an increased risk of GVHD, hence **irradiated blood** is indicated. نقل دم لمریض زارع کلی فی مصر .... لازم یكون دم مشعشع ومفلتر.

NB: Leukocyte depleted blood is already the standard of care in the UK.

### **Recurrence of renal pathologies post-renal transplantation:**

- 1) **Membranoproliferative GN: 40-90%** recurrence rate, type 2 much greater than type 1).
- 2) FSGS: 40%.
- 3) Membranous GN: 30%.

### **CMV infection post-renal transplantation:**

It is very likely that the transplanted kidney has come from a **CMV positive donor**.

Symptoms of CMV infection post transplantation can appear **anytime from 6-60 days after surgery**, and are characterized by **pyrexia**, **flu** like symptoms or an **infectious mononucleosis** type picture (sore throat and pharyngitis).

TTT: **IV Ganciclovir**.

Kidney transplant recipients have a high risk of developing **non-melanoma skin cancer**, so cancer surveillance is an important consideration in kidney transplant recipients.

The patient may have a **malignant melanoma** with **liver metastases**, hence the deranged liver function tests and liver capsule pain. The patient is often **unaware** of the melanoma lesion, and the primary lesion may in fact **disappear** as the disease progresses.

EX: Pt post renal TX has RUQ pain with highly elevated LFTs

## Nephrotic syndrome

It is a Triad of:

- 1. Proteinuria (**> 3g/24hr**) causing
- 2. Hypoalbuminaemia (< 30g/L) and
- 3. Oedema

Loss of antithrombin-III, proteins C and S and an associated rise in fibrinogen levels predispose to thrombosis.

Loss of thyroxin-binding globulin lowers the total, but not free, thyroxine levels.

**Causes** of nephrotic syndrome:

### **1) Primary glomerulonephritis accounts for around 80% of cases:**

- 1) **Minimal** change glomerulonephritis (causes 80% in children, 30% in adults)
- 2) **Membranous** glomerulonephritis
- 3) **FSGS** Focal segmental glomerulosclerosis
- 4) **Membranoproliferative** glomerulonephritis

### **2) Systemic disease (about 20%):**

- DM
- SLE
- Amyloidosis

### **3) Drugs:**

- **Gold (Sodium aurothiomalate) (auranofin).**
- **Penicillamine.**

Nephrotic syndrome > drug causes >> Gold (Sodium aurothiomalate) (auranofin) & Penicillamine.

Removal of Gold therapy in RA often leads to a significant improvement in the degree of proteinuria.

### **4) Others:**

- Congenital
- Neoplasia: carcinoma, lymphoma, leukaemia, myeloma
- Infection: bacterial endocarditis, hepatitis B, malaria

**NB:**

**Nephrotic syndrome - malignancies cause membranous glomerulonephritis**

- Patients with underlying malignancies such as lung, colon and gastric cancer may develop nephrotic syndrome as a Paraneoplastic complication. There appears to be an association with HLA-DR3.
- **Lymphomas** tend to be associated with minimal change disease.

**Complications** of nephrotic syndrome:

- ↑ Risk of **infection** (especially **pneumococcal** infections) due to urinary IgG loss, reduced complement function and decreased splanchnic blood flow.
- ↑ Risk of **thromboembolism (DVT/PE)** due to:
  - **Loss of anti-thrombin III (AT III)** and plasminogen in urine.
  - With **increased** fibrinogen and increased factor VIIIc.
  - Intravascular volume depletion (exacerbated by diuretics).
- **Hyperlipidaemia**.
- **Hypocalcaemia** due to loss of vitamin D and binding protein in urine.
- **ARF** due to renal vein thrombosis which occurs in **10-20%** of patients with nephrotic syndrome (loin pain + haematuria): initial investigation is US: swollen oedematous kidney more than other side, ttt: long term anticoagulation.

Any patient with nephrotic syndrome, then develop **flank pain, haematuria, worsening creatinine, proteinuria** and LL oedema >> **Renal vein thrombosis**

**EX:** female pt. with **SLE (membranous GN)** with **nephrotic range proteinuria** and generalized oedema, develop bilateral **loin pain, tenderness, fever** and **haematuria** >>> **Renal vein thrombosis**.

Diagnosis: Duplex US renal veins, CT or MRV.

TTT: mobilisation, avoid volume depletion, anticoagulation.

**EX:** Old female 77 years old with **DVT** and **nephrotic syndrome (membranous)** >>> the most **direct link** between her DVT and membranous nephropathy is: **1) Antithrombin deficiency, 2) underlying malignancy**.

**Important points in TTT of nephrotic syndrome:**

- Restrict dietary Na.
- Lasix.
- Prophylactic LMWH.
- High dose prednisolone is useful in minimal change disease.
- High protein diet is not beneficial.
- Albumin IV produces only a transient rise in serum levels.

- Prophylactic antibiotics are not recommended, however vaccinations e.g. pneumococcal vaccine can be used.

**NB: Nephritic syndrome consists of:**

- Oliguria
- Acute renal failure
- Haematuria
- Hypertension
- Proteinuria
- Oedema

Outcome and treatment of nephritic syndrome depends on renal biopsy.

**Glomerulonephritides**

Knowing a few key facts is the best way to approach the difficult subject of glomerulonephritis:

- 1) Minimal change disease:
- 2) Membranous glomerulonephritis:
- 3) IgA nephropathy (Berger's disease, mesangioproliferative GN)
- 4) Diffuse proliferative glomerulonephritis
- 5) Focal segmental glomerulosclerosis (FSGS):
- 6) Rapidly progressive glomerulonephritis (crescentic GN)
- 7) Mesangiocapillary glomerulonephritis (membranoproliferative):

**1) Minimal change disease:** (See later)

- Typically a child with nephrotic syndrome (accounts for 80%)
- Causes: Hodgkin's, NSAIDs
- Good response to steroids

**2) Membranous glomerulonephritis:** (See later)

- Presentation: proteinuria / nephrotic syndrome / chronic kidney disease
- Cause: infections, rheumatoid drugs, malignancy
- 1/3 resolve, 1/3 respond to cytotoxics, 1/3 develop chronic kidney disease

**3) IgA nephropathy (Berger's disease), mesangioproliferative GN:** (See later)

- Typically young adult with haematuria following an URTI



**4) Diffuse proliferative glomerulonephritis:**

- Classical post-streptococcal glomerulonephritis in child
- Presents as nephritic syndrome / acute kidney injury
- Most common form of renal disease in SLE (class 4)

**Diffuse proliferative glomerulonephritis, causes:**

- Post-streptococcal
- SLE (class 4)

**5) Focal segmental glomerulosclerosis (FSGS):**

- May be idiopathic or secondary to HIV, HBV, IV drug abuser, and heroin.
- Presentation: proteinuria / nephrotic syndrome / CKD.
- It leads to chronic renal failure in 50% of cases.
- It accounts for approximately 20% of cases of nephrotic syndrome in children and 40% in adults.
- It is one of the most common primary glomerular disorders causing ESRD.
- **A significant number of patients with FSGS go on to ESRD.**
- Unfortunately, **FSGS recurs in 40% of renal transplants** ☹
- Early in the disease course, glomerulosclerosis involves a minority of glomeruli (focal) and only a portion of the glomerular globe (segmental). As the disease progresses more widespread glomerulosclerosis develops.
- Causes:
  - **Idiopathic** (in 80%)
  - Secondary to other renal pathology e.g.
    - Familial (due to mutations in specific podocytes genes),
    - Viral (HIV, HBV, parvovirus B19, CMV, EBV),
    - Drug-induced (Heroin, IFN, lithium, pamidronate, anabolic steroids, calcineurin inhibitors),
    - Adaptive (unilateral renal agenesis, HTN, sickle cell anaemia, vaso-occlusion).
    - IgA nephropathy,
    - Reflux nephropathy
    - Alport's syndrome

Approximately **50% of subjects with FSGS** do not respond to steroid therapy but **ACEIs** are a recognised strategy to slow the progression of renal disease. If FSGS is glucocorticoid resistant, therapy is with a **calcineurin inhibitor**. In HIV associated FSGS, HAART is associated with a reduction of proteinuria.

**6) Rapidly progressive glomerulonephritis (crescentic glomerulonephritis):**

- Rapid onset, often presenting as acute kidney injury
- Causes include Goodpasture's, ANCA positive vasculitis

**Rapidly progressive glomerulonephritis, causes:**

- Goodpasture's
- ANCA positive vasculitis : Wegener's

**7) Mesangiocapillary glomerulonephritis (membranoproliferative):**

- Type 1: cryoglobulinaemia, hepatitis C >>>>> low **C4**
- Type 2: partial lipodystrophy >>>>>low **C3**

Overview:

- Also known as mesangiocapillary glomerulonephritis
- May present as nephrotic syndrome, haematuria or proteinuria
- Poor prognosis

Type 1:

- Accounts for 90% of cases
- Sub-endothelial immune deposits of electron dense material resulting in a 'tram-track' appearance
- Cause: cryoglobulinaemia, hepatitis C ( with ↓ **C4**)

Type 2 - 'dense deposit disease' (DDD):

- Intra-membranous deposits of electron dense material.
- Causes: partial lipodystrophy, factor H deficiency
- Reduced serum complement ( ↓ **C3**)
- C3b nephritic factor (an antibody against C3bBb) found in 70%

Type 3:

- Causes: hepatitis B and C

Management:

- Steroids may be effective

**Minimal change disease**

Minimal change disease nearly always presents as nephrotic syndrome, accounting for 75% of cases in children (peak incidence 2-3 years of age) and 25% in adults.

Nephrotic syndrome in children / young adults - minimal change glomerulonephritis

The majority of cases are idiopathic, but in around 10-20% a cause is found:

- Drugs: NSAIDs, rifampicin
- Hodgkin's lymphoma, thymoma
- Infectious mononucleosis

Pathophysiology:

- T-cell and cytokine mediated damage to the glomerular basement membrane → polyanion loss
- The resultant reduction of electrostatic charge → increased glomerular permeability to serum albumin.

Features:

- Nephrotic syndrome
- Normotension (hypertension is rare)
- Highly selective proteinuria\*
- Haematuria is rare
- Renal biopsy:
  - Light microscopy: NORMAL
  - Electron microscopy shows **fusion of podocytes** with normal Basement membrane.

Podocytes fusion is seen in minimal change GN but may occasionally be a feature of FSGS as well. Minimal change however is far more common.

Management:

- Majority of cases **(80%)** are **extremely steroid responsive** and achieving remission **within 8 weeks** with **prednisolone 60 mg daily**.
- Cyclophosphamide is the next step for steroid resistant cases.
- **Anticoagulation** with LMWH as ATIII deficiency is likely as nephrotic often lose antithrombin in the urine and patient is liable to DVT/PE or renal vein thrombosis.

This boy should be started **on prednisolone 60 mg per day daily for 4 to 6 weeks**, reducing to **40 mg per alternate day for a further 4 to 6 weeks**. With this regime, 93% of children respond with complete loss of proteinuria within 8 weeks.

Prognosis is overall good, although relapse is common. Roughly:

- 1/3 have just one episode
- 1/3 have infrequent relapses
- 1/3 have frequent relapses which stop before adulthood

In children, **30 to 40%** achieve **spontaneous remission** and **90%** achieve remission following 8 weeks treatment with high dose steroids.

However in adults only around **50%** achieve remission.

\*only intermediate-sized proteins such as albumin and transferrin leak through the glomerulus

### **Membranous glomerulonephritis**

- Membranous glomerulonephritis is the **commonest** type of GN in adults.
- It usually presents with **nephrotic** syndrome or proteinuria.
- It accounts **20-30%** of **adult's nephrotic** syndromes.
- It is the **third** most common cause of ESRF (after FSGS).
- **Elderly** in the over **40 age** group patients, **Male twice** than female (**2:1**).

Renal biopsy demonstrates:

- **Light** microscopy: The capillary walls are thickened. Sub epithelial deposits are seen.
- **Electron** microscopy: the glomerular basement membrane is **thickened** with sub epithelial electron dense deposits (monotonous **granular** deposits of **IgG** and **C3**). This creates a 'spike and dome' appearance.

Causes:

- 1) **Idiopathic**: in **60 %** of cases.
- 2) **Infections**: **HBV**, **HCV**, **HIV**, **Malaria**, **Syphilis**, **Leprosy**, **schistosomiasis**.
- 3) **Autoimmune** diseases: **RA**, **SLE** (**class V 5 disease**), **Thyroid**.
- 4) **Drugs**: **Gold**, **penicillamine**, **NSAIDs**, **Captopril**, **heavy metals** e.g. **mercury**, **cadmium**.

- 5) **Malignancy:** lung cancer, leukaemia, lymphoma, melanoma, breast, stomach, colon, prostate (in fact **only 5-10%** of cases are associated with an underlying cancer).
- 6) **Sickle** cell disease.
- 7) **DM**

Prognosis - rule of thirds:

- 1/3: spontaneous remission
- 1/3: remain proteinuric
- 1/3: develop ESRF within 10 years of diagnosis

Management:

- Corticosteroids alone have not been shown to be effective.
- A combination of corticosteroid + another agent such as chlorambucil and cyclophosphamide is often used.
- Blood pressure control: ACEIs have been shown to reduce proteinuria.
- Consider anticoagulation.

**NB:** Corticosteroids by themselves have not been shown to be effective in membranous glomerulonephritis. **ACE inhibitors** have however been shown to reduce proteinuria.

**EX:** Male pt. 50 years old chronic heavy smoker with several episodes of haemoptysis, he is grossly oedematous, ascites, Hb=10, Creatinine=180, albumin=22. Urine protein +++, 5 gm proteinuria/day >>>? **Bronchial carcinoma** with **membranous GN** >> **BX: thickened glomerular BM with deposits of IgG and C3.**

## IgA nephropathy

Basics:

- Also called **Berger's** disease or **mesangio-proliferative** glomerulonephritis.
- It is the **commonest** cause of glomerulonephritis **worldwide**.
- IgA nephritis is most common **during the 2nd and 3rd decade** of life.
- It commonly occurs **within 2 days** of an onset of an **URTI** (sore throat, pharyngitis), or less commonly infection of other mucous membranes (e.g. GI, bladder, and breast).
- The term **syn-pharyngitic nephritis** is sometimes used referring to the onset of haematuria and sore throat virtually simultaneously.

- It should be diagnosed by a **renal biopsy**, it is the investigation of choice to confirm the diagnosis, where IgA is seen deposited in the mesangium (**mesangial IgA deposition**).
- Thought to be caused by mesangial deposition of IgA immune complexes.
- It would seem reasonable to measure serum IgA levels, as these are usually elevated in IgA nephropathy, but raised IgA levels are not specific for the condition.
- There is considerable pathological **overlap with HSP** (arthritis, rash, abdominal pain and nephritis).
- Biopsy: **Mesangial proliferation**.
- Histology:
  - **Light: Mesangial hypercellularity** and extracellular matrix expansion.
  - **E/M: Positive immunofluorescence for IgA & C3.**

Differentiating between IgA nephropathy and **post-streptococcal glomerulonephritis**:

- 1) Post-streptococcal glomerulonephritis is associated with **low** complement levels (**C3**).
- 2) Main symptom in post-streptococcal glomerulonephritis is **proteinuria** (although haematuria can occur).
- 3) There is typically an **interval (weeks)** (e.g. **1 to 3 weeks**) between URTI and the onset of renal problems in post-streptococcal glomerulonephritis.
- 4) **Humps** in the subepithelial space on electron microscopy. (NB: Not all cases of post-streptococcal GN require a biopsy).
- 5) A **wire-loop lesion** is a capillary loop with immune complex deposition circumferential around the loop is seen by light microscopy.

Presentations:

- **Young male** (in their 20s and 30s.), 3 times more common in **males**.
- **Recurrent** episodes of **macroscopic** haematuria (The urine may be frankly bloody or may be the colour of cola. There are no clots in the urine and the haematuria is generally **painless** although some patients complain of mild loin pain), It tends to settle spontaneously within 5 days although the episodes may be recurrent lasting for 1 to 2 years.
- Typically associated with mucosal infections **within 24-48 hours** e.g., **URT** (**sore throat, pharyngitis**).
- It may also present with proteinuria, microscopic haematuria, renal failure or hypertension.
- Nephrotic range proteinuria can occur but rare in only 5%.
- Good prognosis is associated with normal BP, renal function and absence of proteinuria at presentation.

Associated conditions:

- 1) **Alcoholic** cirrhosis
- 2) **Coeliac** disease/dermatitis herpetiformis

Management:

- **No specific treatment is available.**
- The treatment of IgA nephritis is **variable**.
- In a patient with haematuria only, the treatment is **conservative**.
- If the proteinuria is <3 g/day a **ACEIs** can be used to reduce progression of proteinuria and worsening of creatinine.
- When there is nephrotic range proteinuria (>3 g/day) an 8-12 week course of **prednisolone** should be prescribed.
- Steroids/immunosuppressant not be shown to be useful except if there is **rescueric nephritis** on biopsy >>> **IV pulse steroid + cyclophosphamide**.

<b>IgA nephropathy with crescent formation &gt;&gt;&gt; IV Pulse Steroid</b>
--

Prognosis:

- **30%** of children will have a **spontaneous remission within 10 years**.
- **25%** of patients develop **ESRF within 20 years**.
- Markers of good prognosis: frank haematuria.
- Markers of poor prognosis: male gender, proteinuria (especially > 2 g/day), hypertension, smoking, hyperlipidaemia, ACE genotype DD.
- Where ESRD does occur, renal transplantation carries a high chance of success.

<b><u>EX:</u></b> A <b>25-year-old</b> man developed <b>bilateral loin pain</b> and <b>frank haematuria</b> .
---

His symptoms had started **24 hours after** developing a sore throat.

BP was 138/88 mmHg. Urinalysis was positive for blood (4+) and protein (2+).

The most likely diagnosis >>> **IgA nephropathy, NOT** post-strept GN

<b><u>EX:</u></b> A <b>26-year-old</b> female who is <b>13 weeks pregnant</b> has a sustained <b>BP</b> of 170/92 mmHg. She has no past medical history of note and has otherwise been well and asymptomatic. This is her first pregnancy.
--

Examination is otherwise generally normal and no abnormalities are noted on fundoscopy. Ultrasound examination of the kidneys showed both kidneys to be of equal size of 9-10 cm. **Urinalysis reveals protein (+) and blood (+).**

What is the most likely cause of her hypertension >>> **IgA nephropathy.**

TTT: **Oral labetalol** is the safest agent to use in the first and second trimester of pregnancy.

Explanation:

- At 13 weeks of pregnancy, it is too early to present with pre-eclampsia.
- Fibromuscular dysplasia does not typically present with dipstick haematuria.
- Membranous GN is associated with a nephrotic syndrome and therefore one would expect more proteinuria and no haematuria.
- This patient has normal sized kidneys, which would be unusual for reflux nephropathy.
- IgA nephropathy can present with all the above features.
- Beta blockers may cause intrauterine growth retardation.
- ACE inhibitors or ARBs may cause congenital abnormality.
- Manufacturers recommend avoidance of hydralazine.

**NB:** The most common cause of **macroscopic haematuria** in a **child** is **IgA nephritis**.

**NB:** In old patient >>> Renal / bladder cancer.



**Henoch-Schonlein purpura (HSP)**

- Henoch-Schönlein purpura (HSP) is an **IgA** mediated **small vessel vasculitis**.
- There is a degree of overlap with IgA nephropathy (Berger's disease).
- 90% of cases occur in children 2-10 years but can occur in **any age group**.
- HSP is usually seen in children following an infection such as group A Streptococci and Mycoplasma.
- In children, HSP is the most common cause of vasculitis affecting the kidneys.
- The diagnosis can be easily missed, a high degree of suspicion is required.

**Features (4):**

- 1) Palpable purpuric rash (with localized oedema), due to cutaneous vasculitis, over buttocks and extensor surfaces of arms and legs.
- 2) Abdominal pain due to gut vasculitis, which may be severe in some cases, leading to bloody diarrhoea.
- 3) Polyarthritis: especially large: Hips, ankles and knees.
- 4) Features of IgA nephropathy may occur e.g. painless macroscopic/microscopic haematuria, proteinuria, and renal failure.

**Treatment:**

- HSP is a **self-limiting vasculitis**
- Treatment of nephropathy is generally **supportive**.
- All patients with HTN and/or proteinuria should be started on a **ACEIs**.
- Analgesia for arthralgia.
- Once the BP has been controlled or if there were worsening renal function or proteinuria, she should have a **renal biopsy**, and if this showed changes of a **crescentic** glomerulonephritis (GN), then an immunosuppression regime similar to that used in renal vasculitis should be started (probably with high dose steroids in the first instance +/- cyclophosphamide).
- There is inconsistent evidence for the use of steroids and immunosuppressant

**Prognosis:**

- Usually excellent, HSP is a self-limiting condition, especially in children without renal involvement

- It usually settles between 4 to 6 weeks without sequelae if kidney involvement is mild.
- Around 1/3rd of patients have a relapse.

### Glomerulonephritis and low complement (5)

Immune complex Glomerulonephritides can be classified based on normal or decreased C3.

Proteinuria points to glomerular pathology. Glomerular diseases with low complement levels narrow down the differential diagnosis.

Disorders associated with glomerulonephritis and low serum complement levels:

- 1) **Post-infectious** glomerulonephritis (e.g. post streptococcal GN).
- 2) Subacute bacterial **endocarditis** (Low C3 and C4)
- 3) **SLE** (Low C3 and C4)
- 4) **Mesangiocapillary (membranoproliferative) GN** (low C3, normal C4)
- 5) **Cryoglobulinaemia** (Low C3 and C4)

<b>IgA nephropathy is with normal C3</b>
--

### Goodpasture's syndrome (Anti-GBM Disease)

- Goodpasture's syndrome is rare condition associated with both pulmonary haemorrhage and rapidly progressive glomerulonephritis.
- Goodpasture's syndrome is more common in men (sex ratio 2:1) and has a bimodal age distribution (peaks in 20-30 and 60-70 age bracket).
- It is associated with HLA DR2 and HLA-B7.
- Although many diseases can present with these symptoms, the name Goodpasture's syndrome is usually reserved for the autoimmune disease triggered when the patient's immune system attacks Goodpasture's antigen (a **type II hypersensitivity reaction**) which is found in the kidney and lung causing damage to these organs.
- It is caused by anti-glomerular basement membrane **(anti-GBM) antibodies** against type **IV** collagen.
- 30% of patients had positive ANCA serology (**p-ANCA** and is directed against myeloperoxidase).

Features:

- Pulmonary haemorrhage, hemoptysis
- Followed by **RPGN (crescentic)**

Factors which increase likelihood of pulmonary haemorrhage:

- Young males
- Smoking
- Lower respiratory tract infection
- Pulmonary Oedema
- Inhalation of hydrocarbons

Investigations:

- Renal biopsy: **linear IgG deposits** along basement membrane
- **Raised transfer factor** secondary to pulmonary haemorrhages
- **Lung biopsy**: accumulation of hemosiderin laden macrophages with alveoli.

Management:

Where there is **severe hemoptysis**, **rapid removal of Anti-GBM antibody** is indicated, and the **best** way to do this is by **Plasmapheresis** at a specialist center and this is usually **accompanied by pulse therapy of IV methylprednisolone and cyclophosphamide**.

- 1) **Plasma exchange**: daily or on alternate days for 2 to 3 weeks, this will remove the circulating antibody, response is assessed by monitoring symptoms and anti-GBM antibody titres.
- 2) Immunosuppressants by **Steroids** and **Cyclophosphamide** for 6 to 9 months following remission.
- 3) High dose pulsed methylprednisolone is instituted alongside or soon after plasma exchange has been commenced. This is then followed by cyclophosphamide therapy and high dose oral prednisolone which is very gradually weaned to a lower maintenance dose.
- 4) Rituximab in refractory GBS.

NB:

- The combination of hemoptysis, renal failure and linear IgG deposits points to a diagnosis of Goodpasture's syndrome.
- The ANCA-related nephropathies are associated with crescentic glomerulonephritis.
- Pulmonary Oedema is associated with ↑risk; but Dehydration may ↓ the likelihood of pulmonary haemorrhage.
- Studies reveal that without treatment mortality is as high as 90%.
- Despite treatment the mortality of Goodpasture's is 11% and it has a high morbidity with 60% of patients becoming dependent on dialysis.

- Patients who have lost more than 50% of their renal function at diagnosis, unfortunately progress to long-term renal replacement therapy.

Goodpasture's syndrome:

- Anti-**GBM** Abs.
- Ig**G** deposits.

### **Wegener's granulomatosis (WG)**

Wegener's granulomatosis is a **multi-organ** autoimmune condition, which can be **fatal**, associated with a **necrotizing granulomatous vasculitis**, affecting both the **upper** and **lower** respiratory tract as well as the **kidneys**. It is **rare** with an incidence of 5-10 per million.

The classical **triad** consists of:

- 1) **Necrotising granulomatous inflammation** of the **respiratory tract**.
- 2) **Glomerulonephritis** and
- 3) A **small-vessel vasculitis**.

**Pulmonary** involvement is seen in 95% of cases, and **renal** involvement in 85% of cases.

Features:

- Upper respiratory tract: **epistaxis**, sinusitis, nasal crusting.
- Lower respiratory tract: dyspnoea, **haemoptysis**.
- Saddle-shape nose deformity.
- RPGN ('pauci-immune', 80% of patients).
- Also: vasculitic rash, eye involvement (e.g. proptosis), cranial nerve lesions.

Common manifestations of Wegener's granulomatosis include:

- 1) **Constitutional** symptoms like fevers, night sweats, fatigue, lethargy, weight loss, and arthralgia.
- 2) **Ocular** involvement including conjunctivitis, Episcleritis, uveitis, optic nerve vasculitis, and proptosis.
- 3) **ENT** symptoms like chronic sinusitis, rhinitis, otitis media and hearing loss, subglottic stenosis (leading to stridor and features of extra thoracic airway obstruction on flow-volume loop).
- 4) **Pulmonary** disease, for example, pulmonary infiltrates, cough, haemoptysis, chest discomfort, and dyspnoea.

- 5) **Renal** disease manifests as crescentic necrotising glomerulonephritis.
- 6) **Nervous** system involvement manifests as mononeuritis multiplex, sensorimotor polyneuropathy, cranial nerve palsies, and vasculitis of small to medium-sized vessels of the brain or spinal cord, and granulomatous masses that involve the orbit, optic nerve, meninges or brain.
- 7) **Skin** involvement can lead to palpable purpura or skin ulcers.

**Investigations:**

- Positive ANA.
- **cANCA** positive in > **90%**, pANCA positive in 25%.
- Chest x-ray: wide variety of presentations, including cavitating lesions.
- Renal biopsy: epithelial **crescents** in Bowman's capsule.
- To confirm the diagnosis of pulmonary haemorrhage, ↑ raised KCO.

A **renal biopsy** confirms the diagnosis, and guides treatment, and should be performed prior to starting any long term treatment.

**IV pulse methylprednisolone** may be commenced prior to renal biopsy if clinically necessary.

**Management:**

Initial preferred therapy of Wegener's granulomatosis is **3 days pulse 1 gm IV methylprednisolone + cyclophosphamide** (both induce **remission** in **80-90%** of patients).

- In patients who are unable to tolerate cyclophosphamides, azathioprine or methotrexate may be considered as alternatives.
- IV pulse steroid therapy is later converted to oral prednisolone and a suitable steroid sparing agents.
- Patients on high dose steroid and cyclophosphamide are at increased risk of pneumocystis pneumonia, so **co-trimoxazole** should be considered.
- IVIG.
- Plasma exchange.
- TNF-alpha blocking agents, anti-thymocyte globulin (TTG) and monoclonal anti T-cell antibodies can be used in disease refractory to these agents.
- Rituximab IV (anti CD 20 antibody): in cases of resistant to medical ttt.
- Median survival = 8-9 years.

NB: The combination of pulmonary and renal involvement combined with a history of chronic sinusitis points towards a diagnosis of Wegener's granulomatosis.

NB: A prolonged history of epistaxis or sinusitis is commonly found in Wegener's granulomatosis, which in some patients is also associated with an eosinophilia.

**RPGN (Rapidly progressive Glomerulonephritis)**

It is a disease of the kidney that results in a **rapid decrease in GFR** of at least **50%** over a **short period** (a **few days** to 3 months).

The incidence in UK is about **2** cases per **100,000** persons.

The main pathological finding is **fibrinoid necrosis > 90% of biopsy specimens** with extensive **crescent** formation in at least **50%** of the glomeruli.

These crescents are collections of **epithelial cells** and **macrophages proliferation** within the Bowman's space.

The presence of crescents indicates that **glomerular damage** is rapid and progressive (from onset to ESRD within weeks to months).

The clinical presentation is similar to other GNs, but there is rapid progression to renal failure.

**Immunofluorescence** detects deposits of **IgG** and **C3** in the **glomerular BM**.

There are **3 distributions** of immunofluorescence in crescentic GN:

- 1) **Absent** immunofluorescence.
- 2) **Granular** immunofluorescence.
- 3) **Linear** immunofluorescence.

**Classification of RPGN is as follows:**

<b>Pauci-immune RPGN</b>	<b>Immune complex RPGN</b>	<b>Anti-GBM mediated RPGN</b>
<ul style="list-style-type: none"> <li>➤ Microscopic polyangiitis.</li> <li>➤ Wegener's granulomatosis.</li> <li>➤ Idiopathic crescentic GN.</li> </ul>	<ul style="list-style-type: none"> <li>➤ GN.</li> <li>➤ SLE.</li> <li>➤ Cryoglobulinemia</li> <li>➤ IEC.</li> <li>➤ HBV.</li> </ul>	<ul style="list-style-type: none"> <li>➤ Anti-GBM GN (without lung Hge).</li> <li>➤ Goodpasture's disease (with lung Hge).</li> </ul>

**TTT: Pulse methylprednisolone IV and cyclophosphamide.**

**Early initiation** of high dose of steroids has been associated with improved mortality and more rapid return of kidney function.

Prognosis is **poor** if **initial creatinine > 600 Mmol/l**.

### Acute tubule-interstitial nephritis

Acute interstitial nephritis is characterised by interstitial inflammation and oedema. Left untreated this results in **interstitial fibrosis**.

A **definitive** diagnosis is established by **renal biopsy**, which usually shows interstitial oedema with a heavy infiltrate of inflammatory cells and variable tubular necrosis, although **eosinophiluria** and gallium 67 scanning are also suggestive.

**60-70% of cases** of acute interstitial nephritis are induced by exposure to **drugs**.

The mechanism is via a **delayed T-cell hypersensitivity** or **cytotoxic T-cell reaction**.

This is not typically dose-dependent. Multiple medications have been implicated, and the presentation and laboratory findings vary according to the class of drug involved.

Classic presenting features include **fever**, maculopapular **rash** and **arthralgia**.

Mild **eosinophilia** is common, and **eosinophiuria** is pathognomonic.

The **triad** of a **rash**, **fever** and **eosinophilia** is seen in about **10%** of cases.

#### Agents which are commonly implicated are:

- **Beta-lactam antibiotics** (especially penicillin & methicillin)
- Cephalosporins,
- Vancomycin,
- **Sulphonamides**
- Rifampicin
- Quinolone
- **NSAIDs**
- **Diuretics** (thiazides, furosemide)
- Antivirals (**acyclovir**, foscarnet)
- Phenytoin
- **Allopurinol**, and
- Cyclosporin.
- **Omeprazole**

**EX:** Pt take antibiotics for UTI then after 5 days rising renal chemistry, protein ++, blood ++, ↑ TLC 13, ↑Eosinophils, widespread erythematous rash, pruritis, arthralgia, fatigability>>> **Acute interstitial nephritis** >>> Sure diagnosis by **renal biopsy**.

**Treatment:**

- 1) **Cessation** of the causative offending agent.
- 2) **Corticosteroids (High-dose prednisolone)** can have a beneficial effect it may accelerate recovery and prevent long-term renal damage, especially if initiated early.
- 3) **Dialysis** may be required in severe cases.

In general, the **prognosis** of drug-induced acute interstitial nephritis is **good**, and partial or complete recovery of renal function is normally seen.

**NB:** Post-streptococcal GN appears **2-3 wks** after the acute infection especially skin.

**NB:** Serum sickness is a possibility, but it is much **less** common than interstitial nephritis.

**EX:** Pt with **herpetic encephalitis >>> IV acyclovir >>> renal imp & oliguria >>>** due to **acute interstitial nephritis** and **tubular obstruction**.

**IV doses of acyclovir**, which has relatively low solubility, can lead to **deposition of acyclovir crystals** in the **renal tubules**, resulting in intratubular obstruction and foci of interstitial inflammation. This occurs more often in a dehydrated patient.

The decline in renal function is expected to begin **shortly after** acyclovir therapy, rather than three weeks after therapy.

In some cases, **birefringent needle-shaped acyclovir crystals** can be seen in the patient's **urine** (particularly under **polarised light**), so the urine microscopy may indeed add information.

This condition can be prevented by **prior hydration** and **slow drug infusion**.

**NB:** Pt with URTI and had received antibiotics therapy then after that develop renal impairment, proteinuria, haematuria >>> Think of one of these 3: **IgA nephropathy** or **post-streptococcal GN** or **acute interstitial nephritis**.

**NB: Non-steroidal anti-inflammatory drugs (NSAIDs) may cause:**

- A reversible reduction in the GFR
- Acute tubular necrosis
- Renal papillary necrosis,
- Acute tubulointerstitial nephritis often with heavy proteinuria
- Chronic tubulointerstitial nephritis.



## Diabetic Nephropathy: stages

### Stage 1:

- **Hyperfiltration:** increase in GFR
- May be reversible

### Stage 2 (silent or latent phase):

- Most patients do **not** develop microalbuminuria **for 10 years**
- GFR remains elevated

### Stage 3 (incipient nephropathy):

- **Microalbuminuria** (albumin excretion of 30 - 300 mg/day, dipstick negative)

### Stage 4 (overt nephropathy):

- Persistent **proteinuria** (albumin excretion > 300 mg/day, dipstick positive)
- Hypertension is present in most patients
- Histology shows diffuse glomerulosclerosis and focal glomerulosclerosis (Kimmelstiel-Wilson nodules)

### Stage 5:

- **ESRD**, GFR typically < 15ml/min
- Renal replacement therapy needed

### N.B:

- For the purposes of the MRCP, increase in the glomerular filtration rate (GFR) is most characteristic of stage 1 diabetic nephropathy. It is however known that elevation of the GFR usually persists into stage 2.
- The timeline given here is for type 1 diabetics. Patients with type 2 diabetes mellitus (**T2DM**) **progress through similar stages** but in a different timescale - some T2DM patients may progress **quickly** to the later stages.
- **Diabetic nephropathy** has **greater incidence** in **type 1** DM than type 2.
- The **majority** of patients with **diabetic nephropathy** have **type 2 diabetes**, however this is due to **higher prevalence of type 2**, rather than higher incidence of nephropathy (as incidence is in fact higher in T 1 DM).
- Nephropathy itself is signalled by the excretion of trace amounts of protein

in the urine microalbuminuria.

- The progression of the disease may be attenuated by stringent BP control with ACEIs and strict glycaemic control.
- In **type 1 diabetes** the **chance** of progressing to **ESRD** would be approximately **50%** but in **type 2 diabetics** with diabetic nephropathy it is **15%** be expected to progress to ESRD.

A recent case series demonstrated that there is **worsening of renal function** in up to **45%** of patients who **get pregnant with pre-existing diabetic nephropathy**. Any diabetic female with proven diabetic nephropathy and get pregnant, she has a **45% chance of worsening renal function**.

Recommendations are taken from the **NICE** guidelines on the management of *Chronic kidney disease (CG182)* which state that when **initiating ACEIs therapy** a **25% reduction in the eGFR** or **30% increase in the serum creatinine** is tolerable and should **not** lead to changes in dosing.

ACE inhibitors should also be **stopped** or **dose adjusted** if there is a rise in the serum **potassium** level to greater than **6 mmol/l**.

ARBs produce the same effects as ACEIs in terms of reduction in GFR and rise in creatinine and there is **no benefit** in changing from one to the other should the other class of drug impair renal function sufficiently that it has to be stopped.

Unfortunately a progressive increase in serum creatinine is not unusual in the treatment of diabetic nephropathy. It is likely that the increase in creatinine seen is due to **progression of this patient's intrinsic diabetic renal disease** rather than to any other pathology such as renal artery disease upon which ACEI may have an impact.

As such the recommendation is to **continue the ACEI (Ramipril at maximal tolerated dose 10 mg daily)**, as it is likely still to be having an effect in slowing progression.

## **Haematuria**

The management of patients with haematuria is often difficult due to the absence of widely followed guidelines.

It is sometimes unclear whether patients are best managed in primary care, by urologists or by nephrologists.

The terminology surrounding haematuria is changing. Microscopic or dipstick positive haematuria is increasingly termed non-visible haematuria whilst macroscopic haematuria is termed visible haematuria.

### **Causes of transient or spurious non-visible haematuria:**

- UTI
- Menstruation
- Vigorous exercise
- Sexual intercourse

### **Causes of persistent non-visible haematuria:**

- Cancer (bladder, renal, prostate)
- Stones
- Benign prostatic hyperplasia
- Prostatitis
- Urethritis e.g. *Chlamydia*
- Renal causes: IgA nephropathy, thin basement membrane disease

### **Management**

- Current evidence does not support screening for haematuria.

**The incidence of non-visible haematuria is similar in patients taking aspirin/warfarin to the general population hence these patients should also be investigated as normal.**

Testing:

- Urine dipstick is the test of choice for detecting haematuria
- Urine microscopy may be used but time to analysis significantly affects the number of red blood cells detected

NICE urgent cancer referral guidelines:

- Of any age with painless macroscopic haematuria
- Aged 40 years and older who present with recurrent or persistent urinary tract infection associated with haematuria
- Aged 50 years and older who are found to have unexplained microscopic haematuria

**Renal stones**

Risk factors:

- Dehydration
- Hyperparathyroidism, hypercalcaemia, Hypercalciuria
- Cystinuria (NOT CYSTINOSIS)
- High dietary oxalate
- Renal tubular acidosis
- Medullary sponge kidney, polycystic kidney disease
- Beryllium or cadmium exposure

Risk factors for Urate stones:

- Gout
- ileostomy: loss of bicarbonate and fluid results in acidic urine, causing the precipitation of uric acid

Drug causes:

- Drugs that promote **calcium** stones: loop diuretics, steroids, acetazolamide, theophylline
- Thiazides can prevent calcium stones (increase distal tubular calcium resorption)

**Oxalate stones** are uncommon in dietary excess of oxalate. However enteric oxaluria may occur in a number of disorders in which malabsorption results in excessive colonic absorption of oxalate.

These include:

- Coeliac disease
- Crohn's disease
- Chronic pancreatitis, and
- Short bowel syndrome (e.g. post jejunocolic anastomosis for Crohn's disease).

High fluid intake and calcium carbonate are mainstay of prevention.

**EX:** A 20-year-old boy is admitted with renal colic due to renal calculus.

His mother has a similar history of recurrent calculi.

The most likely explanation for recurrent renal calculi in both mother and child >>>  
**Idiopathic hypercalciuria**

Idiopathic hypercalciuria has a **familial** or **sporadic** pattern.

In the **familial** pattern an **autosomal dominant** inheritance is present.

There is **normal serum Calcium**, BUT **raised urinary excretion of calcium**: increased **24 hrs urinary calcium 18** mmol/24 hr (N: 2.5-7.5).

The type of the disease is identical in affected members of the same family and the typical presentation is of **recurrent urinary calculi**.

**TTT:**

- 1) **High fluid intake** (aim for a daily UOP  $\geq$  2000 ml),
- 2) Reducing his dairy dietary intake he may reduce his GIT absorption of calcium,
- 2) **Thiazide** diuretics reduce renal tubular calcium excretion, and therefore can prevent calcium stone formation,
- 3) Potassium citrate also chelates calcium and is useful in combination with thiazides in those who develop hypokalaemia on diuretics.

**Medullary sponge kidney** is a disorder which can affect part, one or both kidneys, resulting in **ectatic** and **cystic** changes of the medullary and papillary **collecting ducts**.

It is often associated with **calculi**, which can result in pyelonephritis and renal tract obstruction.

Medullary sponge kidney is typically **not inherited** but is a **congenital condition**

The aetiology is **uncertain**, but it is thought to be a developmental abnormality, possibly resulting from tubular or collecting duct obstruction at any early age.

The majority of cases are **sporadic**, although a rare **autosomal dominant** familial form exists with onset in adulthood, and a juvenile autosomal recessive form is also recognised.

Recent research has identified a possible defect in the development of the proton pump mechanism in the kidney.

**Renal stones: imaging**

The table below summarises the appearance of different types of renal stone on x-ray.

Type	Frequency	Radiograph appearance
<b>Calcium oxalate</b>	<b>40%</b>	Opaque
Mixed calcium oxalate/phosphate stones	25%	Opaque
Triple phosphate stones*	10%	Opaque
Calcium phosphate	10%	Opaque
<u>Urate</u> stones	5-10%	Radio- <b><u>lucent</u></b>
<u>Cystine</u> stones	1%	<u>Semi-opaque</u> , 'ground-glass' appearance
<u>Xanthine</u> stones	<1%	Radio- <b><u>lucent</u></b>

**NB:** The most common composition of renal stones in the general population is **Calcium oxalate**, followed by **calcium phosphate**. Together these make up a significant majority of stones.

**NB:** Calcium phosphate stones are seen in renal tubular acidosis (RTA).

**Stag-horn calculi**

- Composed of **Struvite** (**ammonium magnesium phosphate**, triple phosphate)
- Form in **alkaline** urine (classically produced by urea splitting organisms, ammonia producing bacteria such as Ureaplasma urealyticum, Klebsiella and Proteus)
- It involves the renal pelvis and extends into at least 2 calyces.
- TTT: Antibiotics, Urease inhibitors, urine acidification with Vit C.

Renal stones on x-ray

- Cystine stones: semi-opaque
- Urate + xanthine stones: radio-lucent

**Renal stones: management**

**Acute management of renal colic**

Medication:

- The British Association of Urological Surgeons (BAUS) recommend **diclofenac** (intramuscular/oral) as the analgesia of choice for renal colic.
- BAUS also endorse the widespread use of **alpha-adrenergic blockers** to aid ureteric stone passage.

Diclofenac use is now less common following the MHRA warnings about cardiovascular risk. It is therefore likely the guidelines will change soon to an alternative NSAID such as naproxen.

**Imaging:**

- Patients presenting to the Emergency Department usually have a KUB x-ray (shows 60% of stones)
- The imaging of choice is a non-contrast CT (**NCCT**). **99%** of stones are identifiable on NCCT. Many GPs now have direct access to NCCT

**Stones < 5 mm will usually pass spontaneously.**

Lithotripsy and nephrolithotomy may be for severe cases.

**Prevention of renal stones:**

**Calcium stones** may be due to hypercalciuria, which is found in up to 5-10% of the general population.

- High fluid intake
- Low animal protein, low salt diet (a low calcium diet has not been shown to be superior to a normocalcaemic diet)
- Thiazides diuretics (increase distal tubular calcium resorption)

**Oxalate stones:**

- Cholestyramine reduces urinary oxalate secretion
- Pyridoxine reduces urinary oxalate secretion

**Uric acid stones:**

- Allopurinol
- Urinary alkalinization e.g. oral bicarbonate

**Cystinuria**

- It is **Autosomal recessive** disorder (AR) characterized by **recurrent** renal stones in **young** ages.
- Cystinuria is the commonest inborn error of amino acid transport.
- It is due to defect in the membrane transport of Cystine, Ornithine, Lysine, and Arginine. (Mnemonic = **COLA**).
- The **glomerulus is unable to resorb** these amino acids, so **accumulation of Cystine in collecting system** and they are therefore excreted into the urine.
- **NO** functional defects within the glomeruli.
- **NO** Cystine deposits within the Cornea.
- The rBAT gene is responsible, and there are 3 forms distinguished by the pattern of tubular amino acid transport.
- Genetics:  
Chromosome **2**:SLC3A1 gene and Chromosome **19**:SLC7A9.
- Features:  
**Recurrent renal stones** in the form of Cystine stones (which are often bilateral, multiple, and can form staghorn, it is yellow, crystalline, (**semi-opaque** on X-ray).
- Diagnosis: **stone analysis**, **Cyanide-nitroprusside test**.
- Management:
  - Conservative
  - Good hydration (>4 litres / day)
  - D-penicillamine as a chelation therapy.
  - Urinary alkalinization with NaHCO<sub>3</sub> (PH 7.5-8)
  - Cystine stones are **not easily** broken by **lithotripsy**, and therefore percutaneous removal is most often used if they do develop.

The **Cystine stones** are **radio-opaque** due to the presence of **sulphur**.  
On plain film, which is not used as much in the UK any more, they are **radio-lucent**.  
On CT, as with almost all stones, cysteine stones are **radio-opaque**.



### Homocystinuria

- It is rare **autosomal recessive** disorder (AR) caused by **deficiency of cystathione beta synthase**. This results in an accumulation of homocysteine which is then oxidized to homocystine.
- Features:
  - Fine fair hair.
  - Skin: malar flush, livedo reticularis.
  - Musculoskeletal: may be similar to Marfan's syndrome.
  - **Neurological: & Psychiatric:** (in up to 60% of cases): Pyramidal tract symptoms, learning difficulties, mentally retarded, behaviour problem, seizures.
  - **Ocular:** downwards dislocation of the lens  
(**Marfan's has upward dislocation of the lens**).
  - Increase risk of **arterial** and **venous** thromboembolism except coronaries, but may present with MI.
- Diagnosis:
  - Urinary homocystine level.
  - Measuring cystathione synthase activity in liver biopsy.
  - **Cyanide-nitroprusside test.** (Which is also +ve in cystinuria).
- TTT: **Vit B6, folic acid.**

**Homocystinuria is caused by a deficiency of cystathionine beta synthase**

Interestingly, patients with **Down's syndrome** have an **excess** of **cystathionine beta synthase**.

### Renal vascular disease

Renal vascular disease is most commonly due to **atherosclerosis** (> 95% of patients).

It is associated with risk factors such as smoking and hypertension that cause atheroma elsewhere in the body.

It may present as hypertension, chronic renal failure or 'flash' pulmonary oedema. In younger patients however **fibromuscular dysplasia (FMD)** needs to be considered. FMD is more common in young women 30-40 years and characteristically has a 'string of beads' appearance on angiography. Patients respond well to balloon angioplasty.

In 30% of cases the disease is bilateral.

Limb arteries with PVD can be affected by fibromuscular dysplasia, but this occurs only in about 5% of cases.

**Arteriosclerosis (renal artery sclerosis)** is a more common cause of RAS than fibromuscular dysplasia.

**40%** may have **peripheral vascular disease (PVD)** with **intermittent claudication** and there may be **proteinuria**.

Investigation:

- **MRA** (MR angiography) is now the investigation of choice.
- CT angiography.
- Conventional renal angiography is less commonly performed used nowadays, but may still have a role when planning surgery.

**MR angiography (MRA)** should be considered the optimum non-invasive screening test for renovascular disease, and **can be performed safely in patients with CKD stage 3 and 4**.

However, there is increasing concern regarding gadolinium related nephrogenic systemic fibrosis (NSF) and guidelines may therefore change in the future.

**Flash pulmonary oedema, U&Es worse on ACEIs, Asymmetrical kidneys**

>>>>>→

**Renal artery stenosis (RAS)** >>>>>

Do (**MRA**) MR angiography

Current UK guidelines with regard to **CKD recommend referral for further investigation of atherosclerotic renal artery stenosis (RAS)** when there is:

- 4) **Refractory HTN** (BP >150/90 mmHg despite **3** antihypertensive);
- 5) **Recurrent episodes of flash pulmonary oedema despite normal left ventricular function (LVF)**.
- 6) **Rise of >20% serum creatinine or fall of GFR >15% over 12 months** with high clinical suspicion of widespread atherosclerosis, **or during the first 2 months after initiation with a ACEIs or ARBs**.

TTT:

- Stop ACEIs.
- Non-ACEI control of BP like CCBs.
- Start **Aspirin** and **statin**.
- There is little or no benefit of angioplasty in RAS, although it may be appropriate in patients with recurrent episodes of pulmonary oedema.

Any patient with bilateral RAS or stenosis in a solitary functioning kidney is a candidate for **revascularization** procedures.

Renal artery stenosis (RAS) **is a potential cause of hypertension.**

Typically patients are vasculopaths and **poor prognosis (80% mortality at five years)** is related to concurrent coronary disease.

It is almost exclusively caused by atherosclerosis, but other causes include fibromuscular dysplasia, vasculitis and external compression.

Typical ultrasound changes are **asymmetrical kidneys**; the affected kidney **>2 cm smaller** than the unaffected kidney.

**ACE inhibitors are contraindicated** in renal artery stenosis as they inhibit the contraction of the efferent arterioles which promote glomerular filtration in the disease.

**NB:** A rise in creatinine of 15% from baseline is expected with commencement of a ACEIs. A large rise in creatinine > 20% should warrant a search for renal artery stenosis (RAS) given the likelihood of vascular disease.

**NB:** The association of “**flash**” **pulmonary oedema** and **hypertension** in a **young** patient (< **50 years**) with **no obvious cardiovascular** risk factors >>> points towards **fibromuscular dysplasia** >>> TTT: **Angioplasty**.

In pulmonary oedema patients can cough up frothy pink sputum.

**EX:** **Young female 30** years old with **sudden onset breathlessness** while eating dinner with cough and **frothy pink sputum** with **high BP 160/100 mmHg** >>> flash pulmonary oedema with? **Fibromuscular dysplasia**.

**Congenital RAS** is extremely rare and may be associated with **coarctation of the aorta**.

**NB:** When ACEI is started, **non-progressive rise in creatinine of 20-30% is acceptable**, but a **progressive** rise of creatinine > **30%** should prompt consideration of **RAS**.

Guidelines generally suggests **checking** serum creatinine **1 week, 1 month** and **then periodically** after starting ACEIs.

## Rhabdomyolysis

Rhabdomyolysis will typically feature in the exam as a patient who has had a fall or prolonged epileptic seizure and is found to have acute renal failure on admission.

Features:

- Acute renal failure with disproportionately raised Creatinine
- Hypocalcaemia (myoglobin binds calcium, serum calcium is bound to damaged muscle, around 20% of patients become hypercalcaemia during recovery as this bound calcium is remobilised.)
- ↑ CPK
- ↑ Phosphate (released from myocytes)
- ↑ K (because K is released from necrotic myocytes and this is exacerbated in the context of renal impairment and metabolic acidosis).
- Myoglobinuria

Causes:

- Seizure
- Collapse/coma (e.g. **elderly patients collapses at home, found 10 hours later or homeless street person**)
- Ecstasy
- Crush injury
- McArdle's syndrome
- Drugs: statins

**NB: Severe hypokalaemia** is considered as one of the **causes** of **rhabdomyolysis**. Also **severe hypophosphatemia** is considered as one of the **causes** of rhabdomyolysis.

Management:

- IV fluids is the most important management step in the prevention of rhabdomyolysis to maintain good urine output.
- Urinary alkalinization is sometimes used in cases where the urine pH is less than 6.5 despite fluid repletion has been advocated.
- Statins should be avoided in patients with rhabdomyolysis.

Collapse + ARF → Rhabdomyolysis - treat with IV fluids

### Retroperitoneal fibrosis

**Lower back pain** is the most common presenting feature.

Associations:

- Riedel's thyroiditis
- Previous radiotherapy
- Sarcoidosis
- Inflammatory abdominal aortic aneurysm
- Drugs: methysergide

### Papillary necrosis

Causes:

- Chronic analgesia use
- Sickle cell disease
- TB
- Acute pyelonephritis
- DM

Features:

- Fever, loin pain, haematuria
- IVU - papillary necrosis with renal scarring - 'cup & spill'

### Contrast Nephrotoxicity

Contrast nephrotoxicity is defined as a **25% increase in serum creatinine** occurring **within 3 days** of the intravascular administration of contrast media.

Studies have shown that **contrast induced nephropathy** is most likely to occur **48 to 72 hours after** the administration of IV contrast.

According to the latest guidelines, the need for a **gadolinium**-based contrast study should be **carefully** considered in any patient with CKD stage 3 or greater.

There is a high risk for this condition of **nephrogenic systemic fibrosis (NSF)** with potentially **fatal** consequence. Because of a higher dose requirement of gadolinium in angiography, the odds of NSF are even higher for the patient.

This toxicity of gadolinium **cannot be** circumvented by hydration or N-Acetylcysteine; they are considered to be more appropriate for preventing radio contrast-induced nephropathy.

So patient with CKD >>> the **magnetic resonance angiography (MRA)** with **gadolinium** is **not recommended** because it carries **a risk of nephrogenic systemic fibrosis (NSF)**.

About **5%** of patients undergoing **cardiac catheterisation** experience **contrast-induced renal dysfunction**.

**Metformin** should be stopped **24 hrs prior** to coronary angiography and reinstated **48 hrs after** the procedure if renal functions are found to be normal.

**ACEIs** are associated with increased risk of contrast nephropathy, most cardiologists therefore discontinue these prior to the procedure.

Risk factors include:

- Known renal impairment (especially diabetic nephropathy)
- Age > 70 years
- Dehydration
- Cardiac failure
- The use of nephrotoxic drugs such as NSAIDs

Prevention:

- 1) Ensure adequate hydration.
- 2) Stop nephrotoxic medications at least 48 hours prior to the planned procedure (such as NSAIDs and Lasix).
- 3) N-Acetylcysteine (usually given orally) has been shown to reduce the incidence of contrast-nephropathy (**600 mg x 2 x 2**).

There is no evidence that NaHCO<sub>3</sub> reduce the chance of nephrotoxicity.

There is nothing to suggest that changing from oral to an insulin sliding scale to improve glycaemic control can reduce the risk.

**Plasma exchange (Plasmapheresis):**

Indications for plasma exchange:

- 1) Guillain-Barre syndrome
- 2) Myasthenia gravis
- 3) Chronic inflammatory demyelinating polyneuropathy (CIDP).
- 4) Goodpasture's syndrome
- 5) ANCA positive vasculitis e.g. Wegener's, Churg-Strauss
- 6) TTP/HUS
- 7) Cryoglobulinaemia
- 8) Hyperviscosity syndrome e.g. secondary to myeloma.
- 9) Fulminant Wilson disease.

In most conditions **5% albumin** is the plasma substitute of choice (to reduce the risk of pathogen transmission), **except for TTP we should use FFP** where it has a therapeutic role in replacing the missing factor, ADAMTS-13.

**Renal tubular acidosis (RTA)**

All three types of renal tubular acidosis (RTA) are associated with **hyperchloraemic metabolic acidosis (Normal anion gap)**.

**Type 1 RTA (Distal):**

- **Inability to generate acid urine (secrete H<sup>+</sup>)** in distal tubule
- So this results in an inability to acidify the urine >> **serum acidosis**.
- **Alkaline urine** increases the risk of calcium deposition, and therefore nephrocalcinosis is a feature of type 1 RTA.
- Hypercalciuria and hyperphosphaturia occur due to the release of calcium phosphate from bone in order to buffer excess H<sup>+</sup> during acidosis, and the direct effects of acidosis on tubular reabsorption on these ions.
- Subsequent bone demineralisation results in Rickets in children and osteomalacia in adults.
- It causes hypokalaemia which can result in weakness.
- Causes include idiopathic, RA, SLE,  Sjogren's & Sickle cell disease.
- Complications include nephrocalcinosis and renal stones.
- TTT: **HCO<sub>3</sub> replacement** (1-3 mmol/kg/day), however **hypokalaemia** must be **corrected before** the acidosis in order to prevent a further fall in K and the risk of cardiac arrest.

**EX:** A 35-year-old man presents with left **loin pain and haematuria**. He comments that he has had three episodes of similar symptoms in the past. Investigations (Creatinine, Na, K, Ca, VBG, CL, and UA) showed: **Low K** 2.9 mmol/L, **Hyperchloraemic metabolic acidosis** ( $\uparrow$  Cl,  $\downarrow$  HCO<sub>3</sub>), **Urine: pH 6.5**, pus 1+, RBC 1+, Protein 1+. What is the most likely diagnosis >>> **RTA 1**

The presence of **alkaline urine of pH more than 5.5** here, with symptoms suggestive of a **renal tract stone**, means that **type 1 RTA** is the most likely diagnosis.

**EX:** female patient 25 years old known to have **SLE**, she has **acute severe loin pain** with **UTI** and Labs: **low K=3.3**, **metabolic acidosis**, **alkaline urine PH 7.4** >>> **RTA type 1 secondary to lupus**.

### Type 2 RTA (proximal):

- **Usually occurs in infancy.**
- **Decreased HCO<sub>3</sub>- reabsorption in proximal tubule.**
- As the distal tubule functions normally, the **acidosis** is **less** severe than type 1 RTA, and they urine has a pH of less than 5.3.
- It causes hypokalaemia
- Rather than being a solitary defect, type 2 RTA is usually associated with a more generalised dysfunction of tubular cells which manifests as Fanconi's syndrome (phosphaturia, glycosuria, aminoaciduria, uricosuria, tubular proteinuria). Phosphate wasting results in marked bone demineralisation.
- Causes & associations of RTA 2 include:
  - Idiopathic, as part of Fanconi syndrome,
  - Wilson's disease (check Kayser-Fleischer ring),
  - Hereditary fructose intolerance
  - Lowe's syndrome.
  - Cystinosis,
  - Heavy metal poison
  - Drugs: Acetazolamide, outdated tetracyclines and certain chemotherapy.
- Complications include osteomalacia.
- Nephrocalcinosis in NOT a feature in RTA type II.
- TTT: **HCO<sub>3</sub>** replacement + **thiazide**.

### Type 4 RTA (hyperkalaemia):

- It causes **hyperkalaemia**.
- It **is not actually a tubular disorder at all** nor does it have a clinical picture similar to the other RTAs.



- It is associated with normal anion gap metabolic acidosis due to **physiological ↓ in proximal tubular ammonium excretion**.
- It is associated with **hyperkalaemia** as there is a **hypo-reninemic hypo-aldosteronism**, hence **hyperkalaemia** and **hyponatraemia** is more typical.
- **Causes** include:
  1. **DM.**
  2. **Hypo-aldosteronism**
- This Hypoaldosteronism either:
  - Aldosterone **deficiency**: which is either **Primary** vs. **secondary** due to hypo-reninemic (hypo-reninemic hypo-aldosteronism).
  - Aldosterone **resistance**:
    - Drugs: Amiloride, Spironolactone, ACEI, ARBs, Heparin, NSAIDS, Trimethoprim, Pentamidine.
    - Pseudohypoaldosteronism.
    - Structural kidney disease as SLE, amyloidosis.
- **TTT**: it depends on the underlying cause.
  - If there is aldosterone deficiency: **fludrocortisone** can be used.
  - In cases of aldosterone resistance: **dietary K restriction**, **loop diuretics** and **low dose oral NaHCO<sub>3</sub>** can be trialled.

### **Type 3 RTA (juvenile RTA):**

- It is **combined** Proximal and distal RTA.
- Results from **inherited carbonic anhydrase II deficiency (C.A. II Def.)**.
- Mutations in the gene encoding this enzyme give rise to:
  - **RTA.**
  - AR syndrome of **osteopetrosis**
  - **Cerebral calcification**.
  - **Mental retardation**.
- 70% of the reported cases are from the **Maghreb** region of North Africa.

### **Fanconi syndrome**

Fanconi syndrome describes a generalised disorder of renal tubular transport resulting in:

- 1) Type **2 (proximal)** renal tubular acidosis
- 2) **Aminoaciduria**
- 3) **Glycosuria**
- 4) **Phosphaturia**
- 5) **Osteomalacia**

Causes:

- Cystinosis (most common cause in children)
- Sjogren's syndrome
- Multiple myeloma
- Nephrotic syndrome
- Wilson's disease

### **Renal cell cancer (RCC) (Hypernephroma)**

Renal cell cancer is also known as hypernephroma and accounts for 85% of primary renal neoplasms.

It arises from **proximal renal tubular epithelium**.

Associations:

- More common in middle-aged men
- Smoking
- Von Hippel-Lindau syndrome
- Tuberous sclerosis
- Autosomal dominant polycystic kidney disease: incidence of renal cell cancer is only slightly increased.

Features:

- Classical **triad**: **haematuria**, loin **pain**, abdominal **mass**, unfortunately this triad is **only** seen in **10%** of the patients diagnosed with RCC.
- Pyrexia of unknown origin.
- Left varicocele (due to occlusion of left testicular vein secondary to tumour invasion of the renal vein).
- Endocrine effects: may secrete **erythropoietin** (polycythaemia) with ↑Hb in 5%, **parathyroid** hormone (hypercalcaemia), **renin** with HTN in 30%, **ACTH**.
- 25% have metastases at presentation.
- 5-year survival rate is 60-70% in tumours confined to the kidney, dropping to 5% in those with metastases.

Complications:

- **Polycythaemia** (due to erythropoietin secretion).
- **Canon ball metastasis**
- **Hypertension**
- **Hypercalcaemia**.

Management:

- **Radical nephrectomy** for confined disease, unless bilateral tumours or poor renal function.
- Immunotherapy with Alpha-interferon and interleukin-2 have been used to reduce tumour size and also treat patients with metastases.
- Receptor tyrosine kinase inhibitors (e.g. sorafenib, sunitinib) have been shown to have superior efficacy compared to immunotherapy.
- Radiotherapy and chemotherapy have no proven benefit in RCC.
- **Metastatic** renal cell carcinoma:
  - **Nephrectomy** (as it may shrink the metastatic deposits) **and small molecule kinase inhibitor, or**
  - **Radiotherapy** (if not fit surgically).

\*incidence of renal cell cancer is only slightly increased in patients with autosomal dominant polycystic kidney disease

<b>EX:</b> 60 years old male with <b>RCC</b> with <b>a solitary brain metastasis &gt;&gt;&gt; TTT: Nephrectomy and small molecule kinase inhibitor.</b>
---

<b><u>Xanthogranulomatous pyelonephritis:</u></b>
---

It can be <b>difficult</b> to <b>distinguish</b> from RCC.
--

It typically presents with symptoms of <b>fever</b> , <b>weight loss</b> and <b>loin pain</b> .
---

It is more common in <b>diabetics</b> , immunocompromised and with obstructive uropathy.
--

The most common organism is <b>Proteus mirabilis</b> .
--

The definitive treatment is <b><u>nephrectomy</u></b> .
---

### **Von Hippel-Lindau (VHL) syndrome**

It is an autosomal dominant condition resulting from a mutation in the VHL gene, a tumour suppression gene on chromosome 3 leading to (**intracranial**, **eye** and **renal** manifestations):

- Retinal haemangiomas,
- CNS haemangioblastomas (ataxia, dizziness, unsteadiness),
- Phaeochromocytoma (↑BP),
- Renal cell carcinoma (polycythaemia)
- Renal cysts (urine blood +, protein +) and
- Pancreatic cysts.

Diagnosis:

- **MRI brain**
- VHL gene analysis.
- 24 hour VMA (for possibility of Pheochromocytoma).
- Ophthalmology review.

**EX:** Female Pt 36 years old, with frank haematuria, dizziness, unsteadiness, ataxia, visual problems, F/H of death of her mother at age 40 years, ↑BP, ↑ HB%, abnormal accumulation of vessels in fundus examination, normal creatinine, urine blood + protein + >>> ? **VHL syndrome** >>> for **MRI brain** (the next most important step in her investigations).

### **Wilms' tumour (Nephroblastoma)**

Wilms' nephroblastoma is one of the most common childhood malignancies. It typically presents in children **< 5 years of age**, with a median age of 3 yrs. old.

Features:

- Abdominal mass (most common presenting feature)
- Painless haematuria
- Flank pain
- Other features: anorexia, fever
- Unilateral in 95% of cases
- Metastases are found in 20% of patients (most commonly lung)

Associations:

- **Beckwith-Wiedemann syndrome**
- As part of **WAGR syndrome**: Wilms', Aniridia, Genitourinary malformations, mental Retardation.
- Hemihypertrophy
- Around one-third of cases are associated with a mutation in the WT1 gene on chromosome 11

Management:

- Nephrectomy
- Chemotherapy
- Radiotherapy if advanced disease
- Prognosis: good, 80% cure rate

**NB:** Beckwith-Wiedemann syndrome is an inherited condition associated with organomegaly, macroglossia, abdominal wall defects, Wilm's tumour and neonatal hypoglycaemia.

**NB:** The most common metastatic/**secondary** tumour that produce a **solitary round shadow** in chest cavity is **renal** in origin.

### **HIV Nephropathy**

- Renal involvement in HIV patients may occur as a consequence of treatment or the virus itself.
- Protease inhibitors such as indinavir can precipitate intratubular crystal obstruction.
- HIV-associated nephropathy (**HIVAN**) accounts for up to 10% of ESRD cases in the United States.
- Antiretroviral therapy has been shown to alter the course of the disease.

There are **five** key features of HIVAN:

- 1) **FSGS**: with focal or global capillary collapse on renal biopsy.
- 2) Nephrotic range proteinuria
- 3) Normal or large kidneys by US.
- 4) ↑ urea and creatinine
- 5) Normotension

It is surprisingly the BP of patients with HIV nephropathy is usually normal.

### **Haemolytic uraemic syndrome (HUS)**

HUS is generally seen in **young adults** and produces a **triad** of:

- 1) Acute renal failure >> Approximately 5% of patients will develop ESRD
- 2) Microangiopathic haemolytic anaemia
- 3) Thrombocytopenia with normal clotting

Causes:

- 1) Post-dysentery (bloody Diarrhea): classically **E coli 0157:H7** ('Vero-toxigenic', 'entero-haemorrhagic' E-coli) or Shigella dysentery.
- 2) Tumours
- 3) Pregnancy
- 4) Cyclosporine, the Pill
- 5) SLE
- 6) HIV

HUS is characterised by the **sudden onset** of haemolytic anaemia with fragmentation of red blood cells, thrombocytopenia and acute renal failure **after a prodromal illness of acute gastroenteritis often with bloody diarrhoea**.

In HUS **90%** of patients are **children** and a history of **prodromal diarrhoeal** illness is more common.

Toxins produced in the intestine **enter the blood and bind to endothelial cells** in target organs.

**Endothelial cell damage** leads to platelet and fibrin deposition with resultant fragmentation of circulating red blood cells and microvascular occlusion.

**Neurological complications** include (from **confusion** to convulsion and coma): **Stroke, seizure** and **coma** occur in **25%** of patients.

Rarely pancreatitis, and Pleural and pericardial effusions.

Investigations:

- **Fragmented RBCs on blood film:** (shistocytes, acanthocytes, burr cells, helmet cells, etc.).
- CBC: anaemia, thrombocytopenia,
- U&E: acute renal failure
- Stool culture for E-coli

Management:

- Treatment is **supportive** e.g. Fluids, blood transfusion, ttt of hypertension and dialysis if required.
- There is **no** role for antibiotics, despite the preceding diarrhoeal illness in many patients.
- The indications for plasma exchange in HUS are complicated. As a general rule **plasma exchange** is **reserved** for **severe** cases of HUS **not** associated with diarrhoea.

- There is **no** role for antibiotics, steroids or immunosuppressant in HUS.
- **Plasma exchange** may be indicated, particularly in **severe** cases of HUS **not associated with diarrhoea**.

**Major differential diagnosis is:**

1. **Sepsis with DIC** - presents with abnormalities of clotting parameters.
2. **TTP** (Thrombotic Thrombocytopenic Purpura) presents with **pentad** of:
  - 1) Microangiopathic haemolytic anaemia,
  - 2) Thrombocytopenic purpura,
  - 3) Neurologic abnormalities,
  - 4) Fever, and
  - 5) Renal disease.

Thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS) have **overlapping** clinical features and are part of the same spectrum of **microangiopathic disease**, with up to 60% of TTP patients missing at least one component of the classical pentad, and around 30% of HUS patients having neurological symptoms and fever.

Although once considered variants of a single syndrome, recent evidence suggests that the **pathogenesis** of **TTP** and **HUS** is **different**.

Patients with **TTP** there is **lack a plasma protease** (**↓ADAMS TS 13**) that is responsible for the breakdown of von Willebrand factor (vWF) multimers and these accumulate in the plasma. The activity of this protease is normal in patients with HUS.

Until the **test for vWF protease activity** becomes available, differentiation between HUS and TTP is based on the presence of **CNS** involvement in **TTP** and the **more severe renal involvement in HUS**.

**Children** account for **90%** of the cases of **HUS**, while **adults** are more frequently affected with **TTP**.

The **prognosis** is **worse** in **TTP** compared to HUS.

The therapy of choice for **TTP** is **plasma exchange with FFP**.

**Platelets transfusion is not recommended as it increase aggregations.**

**SLE Kidney**

**WHO** classification/ International Society of Nephrology (**ISN**) /Renal Pathology Society (**RPS**) **2003** classification (**6** Classes):

- 1) Class I: normal kidney
- 2) Class II: mesangial glomerulonephritis
- 3) Class III: focal (and segmental) **proliferative** glomerulonephritis
- 4) Class IV: diffuse **proliferative** glomerulonephritis
- 5) Class V: diffuse membranous glomerulonephritis
- 6) Class VI: sclerosing glomerulonephritis

Diffuse proliferative glomerulonephritis (**Class 4**) (**IV**) is the **most common** and **severe** form of renal disease in SLE patients.

It also carries the **worst prognosis** for progression to renal failure.

**TTT: high dose steroids** and **pulses of IV cyclophosphamide**, initially given monthly for 6 months and then quarterly.

Pulsed IV cyclophosphamide appears to be as effective as oral cyclophosphamide but has lower toxicity.

Renal biopsy characteristically shows the following findings:

- Glomeruli shows endothelial and mesangial cells proliferation, 'wire-loop' appearance.
- If severe, the capillary wall may be thickened secondary to immune complex deposition.
- Electron microscopy >> shows subendothelial immune complex deposits
- Immunofluorescence >> granular appearance

Management:

- Treat hypertension
- Corticosteroids if clinical evidence of disease
- Immunosuppressants e.g. azathioprine/cyclophosphamide



**Sterile pyuria**

Causes:

- 1) Partially treated UTI
- 2) Urethritis and sexually transmitted diseases (STD) e.g. Chlamydia
- 3) Renal or genitourinary TB
- 4) Acute glomerulonephritis
- 5) Tubulo-interstitial diseases
- 6) Renal stones
- 7) Cancer: Bladder/renal cell carcinoma in old ages
- 8) Adult polycystic kidney disease
- 9) Analgesic nephropathy
- 10) Appendicitis

**EX: Old male** with **long history** of **loin pain**, **fevers** and occasional **rigors** with **increase urine pus** and **RBCs** with **sterile pyuria >>>? RCC >>> US.**

**Ultrasound scan** of the renal tract would be the **first** investigation of choice, as it is able to pick up **95% of renal cell carcinomas (RCC) greater than 1 cm** in diameter. It would also exclude infective or inflammatory collections within the renal tract.

**EX: Old** Asian man 65 years old with **weight loss**, **sterile pyuria**, **high ESR >>> Renal tract tuberculosis.**

Genitourinary TB develops in approximately **5%** of cases of pulmonary TB and is usually due to **haematogenous** spread to the renal cortex during the primary phase of infection.

The cortical lesion may then ulcerate into the pelvis, ultimately involving the bladder, seminal vesicles and prostate.

Diagnosis is by several early morning urine samples for mycobacterial cultures.

TTT is the same as for pulmonary TB.

### **Cholesterol embolisation**

Overview:

- Cholesterol embolisation is a well-documented complication of coronary angiography.
- Precipitating factors includes: angiography, CABG, anticoagulation and thrombolysis.
- Cholesterol emboli may break off causing renal disease.
- Seen more commonly in arteriopaths, abdominal aortic aneurysms.

Features:

- 1) Renal failure
- 2) Eosinophilia
- 3) Purpura
- 4) Livedo reticularis
- 5) Low C3.
- 6) ↑ESR.
- 7) Urine proteinuria.

### **Prescribing in patients with renal failure**

Questions regarding which drugs to avoid in renal failure are common.

Drugs to avoid in renal failure:

- Antibiotics: tetracycline, nitrofurantoin
- NSAIDs
- Lithium
- Metformin

Drugs likely to accumulate in chronic kidney disease - need dose adjustment:

- Most antibiotics including penicillins, cephalosporins, vancomycin, gentamicin, streptomycin
- Digoxin
- Atenolol
- Methotrexate
- Sulphonylureas
- Furosemide
- Opioids

Drugs relatively safe - can sometimes use normal dose depending on the degree of chronic kidney disease:

- Antibiotics: Ceftriaxone, Erythromycin, Doxycycline, Rifampicin, Clindamycin, Linezolid.
- Diazepam
- Warfarin

### **PD peritonitis**

PD peritonitis is an important complication of peritoneal dialysis.

A **high suspicion for the diagnosis** is required and **empirical treatment** is often started.

**PD fluid WCC of greater than 100/mm<sup>3</sup>** is **diagnostic** of PD peritonitis and should be selected.

A PD fluid **neutrophil** percentage of **greater than 50%**.

Raised serum CRP may be associated but is not necessarily diagnostic.

**10 to 30%** of cases are **culture negative**.

At **20-25%** overall, **coagulase negative Staphylococcus (CoNS)** is the **most** commonly **cultured** organism, it is a skin commensal that opportunistically causes infection through the catheter site.

With improved hygiene and technique, rates of staphylococcal infection are falling.

Intra-abdominal pathology (such as a ruptured viscus) should be considered if more than one organism is grown, especially if Gram negative or anaerobic.

Repeated treatment increases the risk of resistant organisms. This may require loss of catheter and switch to haemodialysis.

Contraindication of PD if patient has colostomy or abdominal surgery with possible adhesions.

TTT:

- **Intraperitoneal (IP) antibiotics** is more effective than IV.
- **IP Vancomycin** is necessary in moderate illness.
- **Oral ciprofloxacin** is added to further broaden coverage.
- **IV Vancomycin** would be appropriate for more severe illness.

DP catheter-related peritonitis >>TTT: **IP Vancomycin + Oral ciprofloxacin**

Persistent or relapsing peritonitis, erosion or protrusion of the cuff around the dialysis catheter may unfortunately necessitate **removal**.

Case series report between **11 to 33%** of patients with **CAPD** peritonitis having **pneumoperitoneum** (AXR: air under diaphragm), the majority of which can be managed **conservatively** >>> **Intraperitoneal (IP) Vancomycin** and **Gentamycin** via the dialysis catheter.

### Phenylketonuria (PKU)

- It is an **autosomal recessive** condition caused by a disorder of phenylalanine metabolism.
- This is due to a **defect** in **phenylalanine hydroxylase**, an enzyme which converts phenylalanine to tyrosine.
- **High levels of phenylalanine** lead to problems such as learning difficulties and seizures.
- The gene for phenylalanine hydroxylase is located on chromosome **12**.
- Phenylketonuria is a quarter as common as congenital hypothyroidism
- The incidence of PKU is 1 in 10,000 live births.

#### Features:

- Usually presents **by 6-12 months** e.g. **with developmental delay**.
- Child classically has **fair hair** and **blue eyes**
- Microcephaly, prominent maxilla, growth retardation and wide-spaced teeth
- Learning difficulties
- Seizures in 25%, typically infantile spasms, over 50% have abnormal EEG.
- Eczema.
- **“Musty” odour to urine and sweat**: secondary to phenyl acetate and phenyl ketone.

#### Diagnosis:

- **Guthrie test**: the “heel-prick test” done at 5-9 days of life (Also look for other biochemical disorders such as hypothyroidism).
- Hyper-phenylalaninaemia, increased urinary Phe metabolites.
- Phenyl pyruvic acid in urine.

#### Management:

- **Restriction of dietary phenylalanine**
- Poor evidence base to suggest strict diet prevents learning disabilities.

- Dietary restrictions are however important during pregnancy as genetically normal fetuses may be affected by high maternal phenylalanine levels.

### Alkaptonuria (Black urine disease)

- Rare inherited genetic disorder of phenylalanine and tyrosine metabolism.
- Autosomal recessive.
- Common in Slovakia and Dominican Republic than in other countries.
- Due to a defect in the enzyme homogentisate 1, 2-dioxygenase, which participates in the degradation of tyrosine.
- There is **deficiency of the enzyme homogentisic oxidase** which is responsible of degradation of homogentisic acid produced from phenylalanine and tyrosine.
- As a result, a toxic tyrosine by-product called **homogentisic acid** (or **Alkapton**) accumulates in the blood and is excreted in urine in large amounts.
- Accumulation of homogentisic acid causes pigmentation of the **urine, sclera** and **connective tissues**.
- Excessive homogentisic acid causes damage to **cartilage** (ochronosis, leading to osteoarthritis) and **heart valves** as well as precipitating as **kidney stones**.
- Kidney stones and stone formation in the prostate (in men) are common and may occur in more than 25% of cases.
- Alkaptonuria is often asymptomatic, but the **sclera may be pigmented** (often only at a later age), and the **skin may be darkened in sun exposed areas** and around sweat glands; **sweat may be colored brown or black**.
- The main symptoms of Alkaptonuria are due to the accumulation of homogentisic acid in tissues. In the joints this leads to **cartilage damage**, especially in the **spine**, leading to **low back at a young age in most cases**. Cartilage damage may also occur in the **hip and shoulder**. **Joint replacement surgery (hip and shoulder)** is often necessary at a relatively young age.
- **Valvular heart disease**, mainly calcification and regurgitation of the aortic and mitral valves, and in severe and progressive cases **valve replacement** may be necessary. Coronary artery disease may be accelerated in Alkaptonuria.
- Homogentisic acid is a **reducing** agent, therefore it gives a **false positive** Glucostix test (**urine glucose +++**) but normal Clinitest.
- A distinctive characteristics of Alkaptonuria is that **ear wax exposed to air turned red or black** (depending on diet) after several hours because of the accumulation of homogentisic acids.
- TTT: **Nitisinone** which suppresses homogentisic acid production, is being studied.

**Benign Prostate Hyperplasia (PBH)**

Risk factors:

- Age: around **50%** of **50** year old men will have evidence of BPH and 30% will have symptoms and around **80%** of **80** year old men have evidence of BPH.
- Ethnicity: **Black** > White > Asian

BPH typically presents with lower urinary tract symptoms (**LUTS**) such as:

- Voiding symptoms (**obstructive**): weak or intermittent urinary flow, straining, hesitancy, terminal dribbling and incomplete emptying.
- Storage symptoms (**irritative**): urgency, frequency, incontinence and nocturia.
- **Post-micturition**: dribbling
- **Complications**: UTI, retention, obstructive uropathy

Management options:

- Watchful waiting
- Medications:  **$\alpha$ -1 antagonists**, **5- $\alpha$  reductase inhibitors**. The use of combination therapy was supported by the medical therapy of prostatic symptoms (MTOPS) trial.
- Surgery: Transurethral resection of prostate (TURP).

 **$\alpha$ -1 antagonists (Ex. Tamsulin, Alfuzocin):**

- ↓ Smooth muscle tone (prostate and bladder).
- Considered **first** line, improve symptoms in **around 70%** of men.
- Adverse effect: dizziness, postural hypotension, dry mouth, depression.

**5- $\alpha$  reductase inhibitors (EX. Finasteride):**

- **Block** the **conversion** of **testosterone** to **dihydrotestosterone (DHT)**, which induce BPH.
- Indications: -1-BPH and -2-Male pattern baldness.
- Unlike the  $\alpha$ -1 antagonists causes a reduction in prostate volume and hence may slow the disease progression.
- This however takes time and symptoms may not improve for **6 months**.
- They may also ↓ **PSA** concentrations by up to 50%.
- Adverse effect (1%): insomnia, depression, erectile dysfunction (impotence), ↓libido, ejaculation problems, gynaecomastia, breast tenderness.

**Prostate cancer**

Risk factors:

- 1) Age (70% of men > 80 years have evidence of it on autopsy).
- 2) Race: African-Americans
- 3) Family Hx
- 4) ↑ Fat in diet

### 5) BPH is not a risk factor

Management:

#### 1) Localised prostate cancer (T1/T2):

Treatment depends on life expectancy and patient choice. Options include:

- Conservative: active monitoring & watchful waiting
- Radical prostatectomy
- Radiotherapy: external beam and brachytherapy

#### 2) Localised advanced prostate cancer (T3/T4):

Options include:

- Hormonal therapy: see below
- Radical prostatectomy
- Radiotherapy: external beam and brachytherapy

#### 3) Metastatic (Disseminated) prostate cancer disease:

- Synthetic GnRH agonist:
  - EX. **Goserelin (Zoladex)**: it provide negative feedback to the anterior pituitary.
  - **Cover initially with anti-androgen** to prevent rise in testosterone.
- Anti-androgen:
  - **Cyproterone acetate**: prevent DHT binding to intracytoplasmic protein complexes.
- Orchiectomy.

**N.B:** Anti-androgen treatment such as Cyproterone acetate should be co-prescribed when starting Gonadorelin analogues due to the risk of tumour flare.

This phenomenon is secondary to initial stimulation of luteinising hormone release by the pituitary gland resulting in increased testosterone levels.

The BNF advises **starting Cyproterone acetate 3 days before the Gonadorelin analogue.**

### **Bladder cancer**

It is a common urological cancer with most cases being **transitional cell carcinoma**.

It has **male: female ratio= 3:1** with **women generally having a worse prognosis** than men.

The most classical presentation is with **total, gross, painless haematuria**.

#### **Associated risk factors:**

- **Smoking**
- **Occupational:** aniline dyes used in printing and textile industry, rubber manufacture.
- **Aromatic amines**
- Prior pelvic radiotherapy.
- Exposure to a urinary metabolite of cyclophosphamide (Endoxan®).
- Schistosomiasis (*S.haematobium*).
- Mutations on 17p13.1, the gene coding for p53, mutations of which are associated with high grade bladder cancer.
- Mutation on 9p15 and 9p16, another tumour suppressor gene associated with low grade and superficial tumours.

**N.B:** There is **NO** significant correlation between bladder cancer and coffee, alcohol consumption, artificial sweetener intake or aspirin ingestion, despite a number of stories in the media suggesting a link.

**NB:** **Old** patient with frank **macroscopic haematuria** >>> **Cystoscopy** to exclude bladder cancer is the **first** investigation **even** with normal US

### **Urinary incontinence (UI)**

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Causes:

- **Overactive bladder (OAB)/urge incontinence:** due to detrusor over activity.
- **Stress** incontinence: leaking small amounts when coughing or laughing.
- **Mixed** incontinence: both urge and stress.
- **Overflow** incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement.



Initial investigation:

- Bladder diaries should be completed for a minimum of 3 days
- Vaginal examination to exclude cystocele
- Urine dipstick and culture

Management depends on whether urge or stress UI is the predominant picture.

If urge incontinence is predominant:

- **Bladder retraining** is the initial intervention of choice (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding).
- Bladder stabilising drugs: **Antimuscarinic** is first-line EX:
  - **Oxybutynin** (Uripin ®),
  - **Tolterodine** (Detrol®) and
  - **Solifenacin** (Vesicare ®).
- Surgical management: e.g. sacral nerve stimulation

If stress incontinence is predominant:

- Pelvic floor muscle training (for a minimum of 3 months).
- Surgical procedures: e.g. retropubic mid-urethral tape procedures.

N.B: Examples of **muscarinic antagonists** used in different conditions include: ipratropium (chronic obstructive pulmonary disease) and procyclidine (Parkinson's disease).

### **Urinary tract infection in adults: management**

#### **Lower urinary tract infections in non-pregnant women:**

- Local antibiotic guidelines should be followed if available.
- 2012 SIGN guidelines recommend **trimethoprim** or **nitrofurantoin** for **3 days**.

**Pregnant women with symptomatic bacteriuria** should be treated with an antibiotic for 7 days. A urine culture should be sent.

**For asymptomatic pregnant women:**

- A urine culture should be performed routinely at the first antenatal visit.
- If positive, a second urine culture should be sent to confirm the presence of bacteriuria.
- **SIGN recommend to treat asymptomatic bacteriuria detected during pregnancy with an antibiotic.**
- A 7 day course of antibiotics should be given
- A further urine culture should be sent following completion of treatment as a test of cure.
- Nitrofurantoin should be avoided near term.

For patients with **sign of acute pyelonephritis** hospital admission should be considered:

- Local antibiotic guidelines should be followed if available.
- The BNF currently recommends a broad-spectrum cephalosporin or a quinolone for 10-14 days.

A 30-year-old woman who is 34 weeks pregnant presents with dysuria and urinary frequency. A urine dipstick is positive for nitrites and leucocytes. The most suitable antibiotic to use >> **Amoxicillin** or **Cephalexin (Keflex®)**.

**Miscellaneous**

- Renal blood flow (**RBF**) is approximately **25%** of cardiac output.
- The '**Fick principle**' can be used to estimate RBF through **clearance**.
- RBF is higher in the **cortex** than medulla as one might expect with the increasing **glomeruli** in this region.
- **Sympathetic** stimuli produce **vasoconstriction** and RBF should be **increased** in response to **hypoxia**.

**Acute renal failure may be distinguished from chronic renal failure by renal size on ultrasound scan (USS).**

**Small kidneys on USS** suggest **chronic renal failure**, **EXCEPT** (the following causes of chronic renal failure can present with normal/enlarged kidneys):

- 1) **Amyloidosis**
- 2) **Polycystic** kidney disease
- 3) **Diabetic** glomerulosclerosis
- 4) **Scleroderma**
- 5) Rapidly progressive glomerulonephritis (**RPGN**)

Contraindications to ACE inhibition include:

- **Pregnancy or wants to start a family**
- **Breast feeding**
- **Significant renal artery stenosis.**
- **Angio-oedema**

**Renal imaging:**

**Renal scintigraphy** with **DMSA scan** (dimercaptosuccinic acid **DMSA**) involves administration of radioactive isotope which is avidly taken up by the renal parenchyma.

This permits the identification of regions of **decreased uptake** that may represent **acute inflammation** (such as **pyelonephritis**) or **renal scarring**, also allows detection of **congenital renal disorder**.

A **small kidney** with **uniform** uptake of DMSA is likely to represent **congenital hypodysplasia**,

Whereas a **focal area** of **reduced** cortical uptake associated with loss of contours is more likely to represent an **infection-related scar**.

So the **best** imaging to identify **renal scarring**, for instance after childhood febrile urinary tract infection >>> Renal **DMSA** scintigraphy.

**Renal DTPA** involves an isotope that is **exclusively filtered by the glomeruli**, and is used to give a "**perfusion index**" and **evaluate excretion** (**obstruction** assessment) of the kidney.

**Voiding cystourethrography (VCUG)** is used to determine whether there is vesicoureteral reflux (**VUR**).

-**Arginine vasopressin (AVP)** acts on the **collecting ducts** increasing permeability to water.

-The **total solute excretion** is approximately **700 mosmol/d**.

- **Na reabsorption** is **mostly** through **active** transport in **the loop of Henle** with only a modest reabsorption facilitated by aldosterone.
- A **10 minutes period** of **hyperventilation** would cause a **respiratory alkalosis** leading to an **increased secretion of bicarbonate** and **retention of hydrogen ions**.
- The **rate of ammonium excretion** is **proportional** to the rate of **hydrogen ion excretion**.

### Renin-angiotensin-aldosterone system (RAAS)

Adrenal cortex (mnemonic **GFR - ACD**):

- Zona **g**lomerulosa (on outside): mineralocorticoids, mainly **aldosterone**.
- Zona **f**asciculata (middle): glucocorticoids, mainly **cortisol**.
- Zona **r**eticularis (on inside): androgens, mainly **d**ehydroepiandrosterone (DHEA).

Adrenal cortex mnemonic>>> **GFR - ACD**

The **adrenal medulla** secretes virtually all the **adrenaline** in the body as well as secreting **small amounts of noradrenaline**. It essentially represents an enlarged and specialised sympathetic ganglion

### Renin:

- An enzyme that is **released by the renal juxtaglomerular cells in response to reduced renal perfusion**.
- **Factors stimulating** renin secretion:
  - 1) **Hypotension** causing reduced renal perfusion
  - 2) **Hyponatraemia**
  - 3) **Sympathetic nerve stimulation**
  - 4) **Catecholamines**
  - 5) **Erect posture**
- Factors reducing renin secretion:
  - Drugs: **beta-blockers, NSAIDs**
- Renin **hydrolyses angiotensinogen to form angiotensin I**.

**Angiotensin II:**

- Angiotensin-converting enzyme (ACE) in the lungs converts angiotensin I → angiotensin II.
- Angiotensin II has a wide variety of actions:
  - Causes **vasoconstriction of vascular smooth muscle** leading to raised blood pressure and **vasoconstriction of efferent arteriole of the glomerulus** → increased filtration fraction (FF) to preserve GFR. Remember that  $FF = GFR / \text{renal plasma flow}$ .
  - **Stimulates thirst** (via the hypothalamus).
  - **Stimulates aldosterone and ADH** release.
  - **Increases proximal tubule  $Na^+/H^+$  activity**.

**Aldosterone:**

- Released by the **zona glomerulosa** in response to raised **angiotensin II, potassium, and ACTH levels**.
- **Causes retention of  $Na^+$**  in exchange for  $K^+/H^+$  in distal tubule.

**Renal Biopsy**

For a routine biopsy there is **no preferable side to biopsy**, but commonly it is the Lt Kidney.

**Coagulation studies** should always be performed prior to renal biopsy due to the risk of bleeding (e.g. in a case of alcohol excess, clotting studies may be deranged).

**Macroscopic haematuria** can occur in up to **10%** of renal biopsies.

**Nephrectomy** is a rare but serious complication of renal biopsy required to control bleeding. It should be consented for that.

NB: The hila of the kidneys lie at the L1 and L2 vertebral levels.

# Rheumatology



**Gout**

Gout is a form of microcrystal synovitis caused by the deposition of monosodium urate monohydrate (MSUM) in the synovium.

It is caused by chronic hyperuricaemia (uric acid > 450 µmol/l).

Serum urate concentrations >7 mg/dl are associated with increased risk of gout.

50% of all attacks and 70% of first attacks affect the first metatarsophalangeal joint.

**Predisposing factors:****1) Decreased excretion of uric acid: (90% of cases of primary gout)**

- Chronic kidney disease
- Lead toxicity
- Pre-eclampsia
- Drugs: diuretics, low dose aspirin, pyrazinamide.
- High alcohol (more than 20 units for men, more than 15 units for women).

**2) Increased production of uric acid:**

- Lesch-Nyhan syndrome:
- Myeloproliferative/lymphoproliferative disorder
- Cytotoxic drugs
- Severe psoriasis

**3) Lesch-Nyhan syndrome:**

- Hypoxanthine-guanine phosphor-ribosyl transferase (HGPRTase) deficiency
- X-linked recessive
- Features: gout, renal failure, neurological deficits, learning difficulties, self-mutilation
- Patients with Lesch-Nyhan syndrome often take allopurinol for life.

**4) Drug causes:**

- Diuretics: Furosemide, Thiazides,
- Low dose ASA.
- Cytotoxic agents: cyclosporine, tacrolimus
- Pyrazinamide

Patients with gout are often clustered with the insulin resistance syndrome known as syndrome X: DM, HTN, hypertriglyceridemia, low HDL, although no evidence indicates the gout or hyperuricaemia cause any of these other disorders.

The relationship between serum uric acid and cardiovascular disease remains controversial.

➤ Low dose aspirin may exacerbate gout but **high dose aspirin is uricosuric**.

- Aspirin in a dose of 75-150mg is not thought to have a significant effect on plasma urate levels.
- The British Society for Rheumatology recommends it should be continued if required for cardiovascular prophylaxis.
- Many of the uricosuric drugs may be detrimental in renal failure and may not be effective.

Gouty joint aspiration >>> **Neutrophils** with **negative** birefringent crystals.

Most patients with hyperuricaemia never develop gout or stones. Treatment of these patients is not considered beneficial or cost-effective, and is therefore generally not recommended. The exception to this is in patients at risk of tumour lysis syndrome, where prophylactic treatment is recommended to reduce the incidence of renal impairment.

**Acute management:**

1. NSAIDs
2. Intra-articular steroid injection
3. Colchicine: is an alternative but has a slower onset of action with main side effect is significant diarrhoea.
4. Rasburicase: it is a recombinant urate oxidase which may be given during acute gout attack to allow allopurinol therapy to be commenced without the initial worsening of symptoms. It is also effective newer therapy in urate nephropathy in patients undergoing chemotherapy for haematological malignancy, it prevent and treat hyperuricaemia associated with tumour lysis syndrome (TLS).

Colchicine: inhibits microtubule polymerization by binding to tubulin, interfering with mitosis. Also inhibits neutrophil motility and activity

**If the patient is already taking allopurinol it should be continued & add NSAIDS**

**Indications for allopurinol:**

- 1) Recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'
- 2) Tophi
- 3) Renal disease
- 4) Uric acid renal stones
- 5) Prophylaxis if on cytotoxics or diuretics
- 6) Patients with Lesch-Nyhan syndrome often take allopurinol for life.



**Allopurinol prophylaxis:**

- Allopurinol should not be started until 2 weeks after an acute attack has settled as it may precipitate a further attack if started too early.
- Initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300 µmol/l
- NSAID or colchicine cover should be used when starting allopurinol

**Gout: start allopurinol if  $\geq 2$  attacks in 12 month period  
And should not be started until 2 weeks after an acute attack has settled**

**Side effects of allopurinol:**

- 0.1-0.4 % allopurinol treated patients develop **allopurinol hypersensitivity syndrome (AHS)**.
- This can present as a **severe multi-organ disease**, with non-blanching purpuric **rash**, **hepatic** and **renal** dysfunction, **eosinophilia**, and vasculitis, and has 20-25% mortality.
- 2% of patients on allopurinol develop itchy maculopapular rashes, and between 5-10% develop GIT dysfunction, and deranged liver function tests (LFTs).
- Risk factors for this include renal impairment, thiazide diuretic use, and recent initiation of allopurinol (weeks/months).
- AHS is caused by the direct toxic effects of oxypurinol, or by T cell activating effects of oxypurinol, allopurinol.
- Patients with AHS should not be rechallenged with the drug.
- Allopurinol **increases the anticoagulant effect of warfarin**
- 20% of patients on allopurinol, who are **prescribed amoxicillin or ampicillin**, develop a **rash**.

**Lifestyle modifications:**

- Reduce alcohol intake and avoid during an acute attack
- Lose weight if obese
- Avoid food high in purines e.g. Liver, kidneys, seafood, oily fish (mackerel, sardines) and yeast products

**NB: Gout in pt. with DM and CKD:**

- **Colchicine** is useful in patients with renal impairment who develop gout as NSAIDs are relatively contraindicated. The BNF advises to reduce the dose by up to 50% if creatinine clearance is less than 50 ml/min and to **avoid** if creatinine clearance is **less than 10 ml/min**.
- Co-codamol 30/500 may be used as an adjunct but would not provide relief as monotherapy.

- Studies have shown that **paracetamol 1 g** combined with **codeine 60 mg** have the best analgesic outcomes (the codeine dose is inadequate if < 60 mg).
- **Prednisolone** is an option but would adversely affect his diabetic control.
- **Prednisolone** can be used instead of NSAIDS if it is contraindicated as in case of renal impairment or elderly with an increased risk of bleeding with warfarin.
- Corticosteroids are highly effective, and can be used where NSAIDs are not tolerated, or in refractory disease (intra-articular, oral, intramuscular, IV).
- If a patient with acute gout and cannot take NSAIDs as he has PUD, so Intra-articular steroid injection is the best alternative.
- NSAIDs should be avoided in elderly patients taking warfarin due to the risk of a life-threatening gastrointestinal haemorrhage.
- If Pt. was on warfarin, whilst anticoagulation is not a contraindication to steroid joint injection it would make this option less attractive and Colchicine will be the drug of choice in this scenario.
- Colchicine had little or no interaction with warfarin but a case series was recently published that suggested INR may be increased in some patients prescribed colchicine, so in patients on warfarin with acute gout >>> 1<sup>st</sup> choice: colchicine and 2<sup>nd</sup> choice is Rasburicase
- **Hyperuricaemia** may be found in **asymptomatic** patients who have **not experienced** attacks of gout.
- Hyperuricaemia **may be associated with hyperlipidaemia and hypertension**. It may also be seen in conjunction with the **metabolic syndrome**.
- If diuretics are being used to treat hypertension an alternative antihypertensive should be considered, but they should not be stopped in the presence of CHF.
- If patient with an acute gout flare up and mild renal impairment >>>
  - 1) **Colchicine** and **increase the dose** to cope with the exacerbation up to a dose of 3 mg divided in 600 Mcg portions.
  - 2) A **short course of corticosteroids** (prednisolone 30 mg daily for 1 week) is a possibility **if** the patient fails to respond to the increased dose of colchicine.
  - 3) Adding NSAID may worsen his kidney function.

### **Pseudogout**

Pseudogout is a form of microcrystal synovitis caused by the deposition of calcium pyrophosphate (CPP) dihydrate in the synovium.

Risk factors:

- Haemochromatosis ( $\uparrow$  transferrin saturation  $> 50\%$ )
- Wilson's disease
- Hyperparathyroidism (ESRD).
- Hypothyroidism
- Acromegaly
- Low magnesium, low phosphate

Features:

- Red, hot, tender joint with effusion.
- Knee, wrist and shoulders most commonly affected
- Joint aspiration: **non- or weakly-positively birefringent rhomboid or rod shaped crystals**
- X-ray: **chondro-calcinosis** (Non-specific changes such as loss of joint space and linear calcification of the articular cartilage).

**NB:** Pseudogout itself may cause (OA) osteoarthritic-like changes.

Management:

- Aspiration of joint fluid, to exclude septic arthritis
- NSAIDs or intra-articular, intra-muscular or oral steroids as for gout.
- Colchicine may be used if NSAIDs are contraindicated as in renal impairment.

**NB:** *Elevated transferrin saturation may indicate haemochromatosis; a recognised cause of Pseudogout. A high ferritin level is also seen in haemochromatosis but can be raised in a variety of infective and inflammatory processes, including Pseudogout, as part of an acute phase response.*

**EX:** A 72-year-old man presents with an **acutely painful right knee**.

On examination, he has a temperature of  $37^{\circ}\text{C}$  with a **hot, swollen** right knee.

Of relevance amongst his investigations, is a **TLC** of  $12.6 \times 10^9/\text{L}$  (4-11) and a knee radiograph which shows **reduced joint space** and **linear calcification of the articular cartilage**.

**Culture** of aspirated fluid reveals **no growth**.

The most likely diagnosis is >>> **Pseudogout**.

DD: Negative synovial fluid culture makes septic arthritis a less likely diagnosis.

DD: It is rare for rheumatoid arthritis to present as a large joint monoarthritis in a gentleman of this age.

## Septic arthritis

### Overview:

- Most common organism overall is **Staphylococcus aureus**
- In young adults who are sexually active Neisseria gonorrhoeae should also be considered.
- Most septic joints have a **white count > 50,000 /Micro L**, with more than 75% **polymorphneuclear leukocytosis**.

### Management:

- Arthrocentesis: Synovial fluid should be obtained before starting treatment
- Gonococci is a Gram negative intracellular diplococci.
- Intravenous antibiotics which cover Gram-positive cocci are indicated.
- The BNF currently recommends flucloxacillin or clindamycin if penicillin allergic.
- Antibiotic ttt is normally be given for several weeks (BNF states 6-12 weeks).
- Needle aspiration should be used to decompress the joint.
- Surgical drainage may be needed if frequent needle aspiration is required.

**NB:** In gonococcal infection: standard aerobic and anaerobic cultures often **fail** to grow the organism; selective media are often required and the organism grows best in an atmosphere containing 3-10% CO<sub>2</sub>.

**NB:** Disseminated gonococcal infection (DGI) with septic arthritis >>> ttt: **IV Ceftriaxone 1 g OD for 7 days**.

**NB:** Joint aspiration is mandatory in all patients with a **single** hot, swollen joint to rule out septic arthritis. If this was excluded in the above patient then intra-articular or system steroid therapy may be considered.

## Reactive arthritis

Reactive arthritis is one of the **HLA-B27** associated seronegative spondyloarthropathies. It encompasses **Reiter's syndrome**, a term which described a classic **triad** of urethritis, conjunctivitis and arthritis following a dysenteric illness during the Second World War.

Later studies identified patients who developed symptoms following a sexually transmitted infection (post-STI, now sometimes referred to as sexually acquire reactive arthritis, **SARA**).

Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint.

Reactive arthritis is a **post-infective autoimmune** condition that is associated with gastrointestinal (Shigella, Salmonella, Campylobacter) and genitourinary infections (Chlamydia). There will be a recent history of gastroenteritis or urethritis.

Symptoms of reactive arthritis typically appear 1-4 weeks following the initial infection

**Urethritis + arthritis + conjunctivitis = reactive arthritis**

Reactive arthritis >>>> **the Pt. can't see, can't pee, can't bend the knee**

Epidemiology:

- Post-STI form much more common in men (e.g. 10:1)
- Post-dysenteric form equal sex incidence

The table below shows the organisms that are most commonly associated with reactive arthritis:

<b>Post-<u>dysenteric</u> form</b>	<b>Post-<u>STI</u> form</b>
<i>Shigella flexneri</i> <i>Salmonella typhimurium</i> <i>Salmonella enteritidis</i> <i>Yersinia enterocolitica</i> <i>Campylobacter</i>	<i>Chlamydia trachomatis</i>

Features:

- Typically develops within 4 weeks of initial infection - symptoms generally last around 4-6 months
- **Arthritis** is typically an **asymmetrical oligoarthritis** of lower limbs, Dactylitis.
- Symptoms of **urethritis**
- **Eye**: conjunctivitis (seen in 50%), anterior uveitis
- **Skin**:
  - Circinate balanitis (painless vesicles on the coronal margin of the prepuce),

- Keratoderma blenorrhagica (palmo-plantar pustulosis) (waxy yellow/brown papules on palms and soles),
- Psoriasiform skin and
- Nail and mucosal lesions

Around **15-50 %** of patients with reactive arthritis have **recurrent** episodes whilst 15-30 % of patients develop chronic persistent arthritis or sacroiliitis.

**Management:**

**First line of TTT of reactive arthritis is oral NSAIDs not antibiotics.**

- Symptomatic: analgesia, **NSAIDS**, intra-articular steroids
- Sulfasalazine and methotrexate are sometimes used for persistent disease
- Symptoms rarely last more than 12 months.
- Antibiotics do not change the course of reactive arthritis, even when an infective cause is identified. However, some studies show that they may help to reduce the length of arthritis, particularly if Chlamydia is the triggering infection.
- If Chlamydia infection is suspected/confirmed >>> ttt by Doxycycline.

**Gonococcal arthritis** is characterized by **dermatitis-polyarthritis-tenosynovitis** syndrome. It is the most common cause of septic arthritis in sexually active adults

**SAPHO syndrome.** سافو

**SAPHO** is an acronym for Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis.

It is characterised by **osteosclerotic bone lesions**, Bone biopsy can reveal sterile osteomyelitis, and a **variety of skin lesions**. The skin lesions are characterised by neutrophilic pseudo abscesses.

- 1) **Synovitis** - may be present rarely, and associates with erosions.
- 2) **Acne** - may be severe (conglobate or fulminans) and recur with new bony involvement.
- 3) **Pustulosis** - palmo-plantar pustulosis occurs in approximately **50%** of patients, other skin lesions may include psoriasis, hidradenitis suppurativa, acne, and rarely Sweet's syndrome.
- 4) **Hyperostosis** (increase in bone substance) and **osteitis** (inflammation of the bones) - the bony lesions typically involve the acromioclavicular, and sternoclavicular joints. Other sites include anterior chest wall, sternum, clavicle, pubic symphysis, spine, and mandible. These lesions are visualised on 99m technetium bone scan or MRI.

The cause of the SAPHO syndrome is **unknown**.

**Diagnosis:**

Should be suspected when there is an **association** of **rheumatic pain** with a **pustular skin disease**.

**Treatment:**

- SAPHO has **no** specific treatment, and some cases remit spontaneously.
- For the arthritic symptoms (i.e. NSAIDs and DMARDs).
- Isotretinoin and aciretin can be used to treat the skin disease.
- In the more severe cases corticosteroids, calcitonin, bisphosphonates and TNF-inhibitors can be used.

**Relapsing polychondritis (RP)**

It is an inflammatory condition that involves **cartilaginous** structures, predominantly those of the ear pinna, nasal septum and larynx.

Attacks are recurring and may last from a few days to several weeks.

There is no gender difference in the distribution of the disease, and although it can occur at any age, it is most common in the fifth decade.

General symptoms include intermittent fever, weight loss, and **sudden onset of ear pain** with an **inability to sleep on the affected site**, **diminished hearing**, monoarthritis or **polyarthritis of both small and large joints**, back pain, myalgia, **mild epistaxis**, saddle-shaped nose, **redness of the eyes** indicative of conjunctivitis, Episcleritis and/or scleritis, **hoarseness of voice** and **recurrent URTI**.

The sternoclavicular, costochondral and sternomanubrial joints are commonly involved. **Costochondritis** can manifest as **pleuritic chest pain**.

Involvement of the tracheal cartilage may result in **tracheal stenosis** and result in life-threatening **stridor**.

There are **no specific diagnostic** laboratory findings, but the non-specific inflammatory markers like ESR and CRP are often elevated.

Biopsy of the affected cartilaginous tissue will confirm the diagnosis.

It is important to investigate for the presence of other concurrent autoimmune disease.

**No** specific therapy exists only symptomatic ttt.

**Rheumatoid arthritis (RA)**

Epidemiology:

- Prevalence in UK = 1%
- The incidence of rheumatoid arthritis is approximately 2.5 per 10 000 per year (1.5 in men and 3.6 in women).
- Peak onset = 30-50 years, although occurs in all age groups
- F:M ratio = 3:1
- Some ethnic differences e.g. high in Native Americans
- Associated with **HLA-DR4** (especially Felty's syndrome).
- RA is associated with several antibodies such as RF, collagen antibody, capable of reaction **at sites other than the joints** (i.e. the disease is not confined to the joints).
- Damage is mediated by several means, including **macrophages** activated by **CD4+ T cells**, and by complement fixing immune complexes.

A number of studies have suggested a link between **Proteus mirabilis** infection and the development of **RA** in susceptible individuals, and this may contribute to the increased incidence of RA in **women**, who are more susceptible to **UTI**.

**Tumour necrosis factor (TNF)**

Rheumatoid arthritis - TNF is key in pathophysiology

TNF is important in the pathogenesis of rheumatoid arthritis.  
TNF blockers (e.g. infliximab, etanercept) are now licensed for ttt of severe RA.

**TNF** is a **pro-inflammatory cytokine** with multiple roles in the immune system.

TNF is secreted mainly by **macrophages** and has a number of effects on the immune system, acting mainly in a paracrine fashion:

- Activates macrophages and neutrophils
- Acts as co-stimulator for T cell activation
- Key mediator of bodies response to Gram negative septicaemia
- Similar properties to IL-1
- Anti-tumour effect (e.g. phospholipase activation)

TNF-alpha binds to both the p55 and p75 receptor. These receptors can induce apoptosis. It also causes activation of NFkB.

Endothelial effects include increase expression of selectins and increased production of platelet activating factor, IL-1 and prostaglandins.



TNF promotes the proliferation of fibroblasts and their production of protease and collagenase. It is thought fragments of receptors act as binding points in serum.

Systemic effects include pyrexia, increased acute phase proteins and disordered metabolism leading to cachexia.

**Contraindications of usage of TNF- alpha antagonist:**

- 1) Active infection
- 2) **Active TB**
- 3) **MS** (Multiple sclerosis)
- 4) Heart failure (NYHA grade 3-4).
- 5) Pregnancy
- 6) Breast feeding

**Rheumatoid factor (RF)**

Rheumatoid factor (RF) is a circulating antibody (usually **IgM**) which reacts with the **Fc** portion of the patients own **IgG**.

Rheumatoid factor is an <b>IgM</b> antibody with reactivity <b>against Fc portion of IgG</b>
--

RF can be detected by either:

- Rose-Waaler test: sheep red cell agglutination
- Latex agglutination test (less specific)

RF is positive in **70-80% of patients with rheumatoid arthritis**; high titre levels are associated with **severe progressive** disease (but **NOT** a marker of disease **activity**).

A positive rheumatoid factor is associated with: ☹

- More severe erosive disease
- Extra-articular manifestations including subcutaneous nodules and
- Increased mortality.

Other conditions associated with a **positive RF** include:

- Sjogren's syndrome (around **100%**)
- Felty's syndrome (around **100%**)
- Infective endocarditis (= **50%**)
- Mixed cryoglobulinaemia (types II and III) (**40 to 100%**)
- SLE (= **20-30%**)
- Systemic sclerosis (= 30%)

- Polymyositis/dermatomyositis - 5 to 10%
- General population (= 5%)
- Rarely: TB, HBV, HIV, EBV, leprosy, syphilis, brucellosis.

In RA, RF is positive in 80% of patients, whereas in Sjogren's syndrome and cryoglobulinaemia, it is prevalent in up to 90% of cases.

### Anti-CCP Ab (Anti-cyclic citrullinated peptide antibodies)

**Anti-CCP antibodies** are associated with rheumatoid arthritis (**highly specific**)

- Anti-cyclic citrullinated peptide antibody may be detectable up to 10 years before the development of rheumatoid arthritis.
- It may therefore play a key role in the future of rheumatoid arthritis, allowing early detection of patients suitable for aggressive anti-TNF therapy.
- It has sensitivity similar to rheumatoid factor (70-80%, see below) with a much higher specificity of 90-95%.
- NICE recommends that patients with suspected RA with RF negative should be tested for Anti-CCP Abs.

### Rheumatoid arthritis: diagnosis

NICE have stated that **clinical diagnosis** is more important than criteria such as those defined by the American College of Rheumatology.

The most commonly used classification criteria are the American College of Rheumatology criteria. These criteria do not perform well in early disease.

### Rheumatoid arthritis is a clinical diagnosis. The classic features are:

- **Symmetrical inflammatory polyarthritis**
- Arthritis affecting the **small** joints of the **hands and feet**.

### Diagnostic tests are:

- **RF**: there are many false positive and negatives.
- **Anti CCP antibody**: more specific for rheumatoid arthritis.
- **ANA**: present in 20-30% of patients with rheumatoid arthritis.

Target population. Patients who

- 1) have at least 1 joint with definite clinical synovitis
- 2) with the synovitis not better explained by another disease

Classification criteria for rheumatoid arthritis (add score of categories A-D; a score of **6/10** is needed definite rheumatoid arthritis)

<b>A. Joint involvement</b>		
	1 large joint	0
	2 - 10 large joints	1
	1 - 3 small joints (with or without involvement of large joints)	2
	4 - 10 small joints (with or without involvement of large joints)	3
	10 joints (at least 1 small joint)	5
<b>B. Serology (at least 1 test result is needed for classification)</b>		
	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
<b>C. Acute-phase reactants (at least 1 test result is needed for classification)</b>		
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
<b>D. Duration of symptoms</b>		
	< 6 weeks	0
	> 6 weeks	1

Key:

- RF = rheumatoid factor
- ACPA = anti-cyclic citrullinated peptide antibody

### Rheumatoid arthritis: x-ray changes

Early x-ray findings:

- **Periarticular (juxta-articular) osteopenia and osteoporosis**
- **Periarticular decalcification**
- loss of joint space
- soft-tissue swelling

Late x-ray findings:

- Periarticular erosions
- Subluxation

\* Periarticular osteopenia and osteoporosis would point towards a diagnosis of (RA).

\* Loss of joint space is common in both RA and OA also in Pseudogout.

In the **early stages of an insidious onset** of the RA disease, the acute phase markers CRP and ESR are often normal, particularly when small joints are involved.

At this stage of early RA >>> the diagnostically most informative test is **hand and feet X-ray >>> periarticular osteopenia and marginal erosions** at affected joints.

**Foot** joints are often radiologically affected **before** hand joints.

### Rheumatoid arthritis: prognostic features

**Poor** prognostic features: ☹

- Rheumatoid factor positive
- Anti-CCP antibodies
- HLA DR4
- **Insidious** onset
- Poor functional status at presentation
- **X-ray: early articular erosions** (e.g. **within the first 6 months of presentation** and in less than < 2 years).
- Extra articular features e.g. nodules
- Female sex.

**NB:** (☺ Acute or Sudden onset is not a poor prognosis)

### Rheumatoid arthritis: management

Patients with evidence of joint inflammation should start a **combination** of disease-modifying drugs (**DMARD**) as soon as possible.

Other important treatment options include analgesia, physiotherapy and surgery.

Initial therapy:

- In NICE guidelines it is recommend that patients with newly diagnosed active RA start **a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids)**
- (EX: Methotrexate + sulfasalazine + short-course of prednisolone)

### **DMARDs:**

- 1) **Methotrexate** is the most widely used DMARD.
- 2) **Sulfasalazine** (500 mg tab)
- 3) **Leflunomide** (Arava® 20 mg tab)
- 4) **Hydroxychloroquine** (HCQ) (plaquenil® 200 mg tab): less effective.

**TNF-inhibitors (Biologic therapy):**

- The current indication for a TNF-inhibitor is an inadequate response to at least two DMARDs including methotrexate
- Adverse effects of TNF blockers include reactivation of latent tuberculosis and demyelination.
- The risk of TB reactivation is most pronounced in the **first 3 months** of ttt.
- The current British Thoracic Society BTS guidelines therefore recommend a clinical examination, chest radiograph and thorough history taken to check for prior TB.
- In the UK, patients have a baseline CXR and assessment of risk of infection with Mycobacterium tuberculosis prior to starting treatment with anti-TNF  $\alpha$ .
- Any patient with an abnormal chest radiograph or previous history of TB should be referred for assessment by a specialist with an interest in TB.
- Those with symptoms raising a suspicion of TB should be thoroughly investigated to exclude active disease.
- Any patient with active TB, either pulmonary or non-pulmonary, should receive standard chemotherapy. They must complete 2 months full treatment before starting anti-TNF alpha treatment.
- Patients with an abnormal chest radiograph consistent with past TB, or a history of prior extra pulmonary TB but who have received previous adequate therapy can be started on anti-TNF alpha therapy but need to be monitored regularly.
- Where there is an abnormal chest radiograph, or a history of prior pulmonary or extra pulmonary TB not previously adequately treated, chemoprophylaxis with isoniazid for 6 months should be given before commencing anti-TNF alpha treatment.
- The BTS guidelines have not been updated to include recommendations regarding Quantiferon Gold test and Elispot tests. Practice does vary between individual NHS trusts regarding who to test with one of these, and which to use. However, the most accepted recommendations are that patients who test positive with either of these should be treated with chemoprophylaxis (either isoniazid for 6 months, or dual therapy Rifampicin + INH for 2 months) at the same time as being started on anti-TNF alpha treatment.
- For patients with a normal chest radiograph who have not started immunosuppressive therapy, a tuberculin test is helpful.

**TNF-inhibitors should be stopped 2-4 wks before any major operation.**

**Stopping earlier may lead to disease flare and thus interfere with the surgery.**

**Treatment may be restarted postoperatively if there is no evidence of infection.**

- Examples of anti-TNF alpha agents:
  - Etanercept,
  - Infliximab,
  - Adalimumab,
- **Etanercept SC:**
  - It is a recombinant human protein, acts as a decoy receptor for TNF- $\alpha$ , it is a fusion protein that mimics the inhibitory effects of naturally occurring soluble TNF receptors.
  - **Dose: 25 mg SC** administration **twice weekly**,
  - It can cause demyelination and risks of TB reactivation.
  - It can be used alone in ttt RA or with methotrexate.
  - Also can be used in psoriasis and psoriatic arthritis.
  - Used with caution in patients with asthma, renal imp.
- **Infliximab IV:**
  - Monoclonal antibody, binds to TNF- $\alpha$  and prevents it from binding with TNF receptors, **IV** administration, risks include reactivation of tuberculosis
  - Infliximab should normally be used in combination with methotrexate and requires IV infusion in a hospital setting.
  - If a patient is intolerant of methotrexate, etanercept (anti-TNF receptor antibody) and adalimumab (humanised anti-TNF antibody) are alternatives to infliximab which can be given as monotherapy.
  - **Infliximab** is also used in **active Crohn's** disease **unresponsive to steroids**.
- **Adalimumab:** monoclonal antibody, SC administration

**Tocilizumab:** (anti-IL 6 receptor).

**Rituximab:**

- Anti-CD20 monoclonal antibody, results in B-cell depletion.
- Two 1g intravenous infusions are given two weeks apart.
- The most common side effects:
  - Allergic reactions: low BP and facial flushing during IV infusion.
  - Flu-like symptoms: high fever, chills, weakness, muscle aches, tiredness, dizziness and headache during IV infusion.
  - Nausea and vomiting.
  - Tumour pain.
- Uses: Non-Hodgkin lymphoma, Pure red cell aplasia, ITP, Evans syndrome, Rheumatoid arthritis, Multiple sclerosis, SLE, Vasculitis.

**Abatacept:**

- Cytotoxic T-lymphocyte antigen 4 (**CTLA 4**) homologue.

- Fusion protein that modulates a key signal required for activation of T lymphocytes
- Leads to decreased T-cell proliferation and cytokine production
- Given as an infusion
- Not currently recommend by NICE

### **Rheumatoid arthritis: complications**

A wide variety of extra-articular complications occur in patients with RA:

- **Cardiac:**
  - **IHD:** RA carries a similar risk to T2DM,
  - **Constrictive pericarditis** (in **30%**)
- **Respiratory:**
  - Pulmonary **fibrosis** (**Fibrosing alveolitis**) >> **progressive breathlessness**,
  - Pleural effusion,
  - Pulmonary nodules,
  - **Bronchiolitis obliterans**,
  - Methotrexate pneumonitis (it is potentially life-threatening and occurs in 1-5% of patients who are treated with methotrexate,
  - Pleurisy,
  - **Caplan's syndrome** (RA + massive fibrotic nodules with pneumoconiosis occupational coal dust exposure).
- **Ocular** (it is common and occur in 25% of patients):
  - **keratoconjunctivitis sicca** (**most common**): (dry, burning and gritty eyes caused by decreased tear production)
  - **Episcleritis** (**erythema only**)
  - **Scleritis** (**erythema and pain**)
  - Corneal ulceration (**Corneal melts** = perforated corneal ulceration).
  - Keratitis,
  - Steroid-induced cataracts,
  - Chloroquine retinopathy
- Osteoporosis
- Increased risk of infections (possibly atypical): CMV-associated colitis.
- Depression
- Skeletal: carpal tunnel syndrome (CTS): paraesthesia in hands that may let him awake from sleep

Less common complications of RA:

- **Felty's syndrome** (Active RA + splenomegaly + low white cell count).

- **Amyloidosis** >>> **Renal failure (Nephrotic range proteinuria)** >>> **high levels of serum amyloid A protein** which is also an acute phase reactant, the kidneys are usually normal size, or slightly large and **hepatomegaly**.
- **AIHA** (autoimmune haemolytic anaemia): **warm** type, **+ve DGT** (direct globulin test) (Coomb's test), spherocytosis, **↑RTX** & **↑LDH**. (see Haematology).

Rheumatoid arthritis: patients have an increased risk of **IHD**

Episcleritis is not painful, Scleritis is painful

*Proteus mirabilis* is a Gm -ve rod, causing **UTI** >>> predispose susceptible pt. to **RA**

### **Felty's syndrome:**

It usually occurs in patients with **long-standing seropositive RA**.

Two third of the patients are **female** (60-70% female predominance).

It is usually recognised from the 5<sup>th</sup> decade onwards in patients who have had RA for an average of 10 years or more.

C/P: **Active RA** + **Leukopenia** + **Lymphadenopathy** + **Splenomegaly** + also **leg ulcers**, **recurrent infections (URTI)** and **Episcleritis** may be present.

**ANA** is positive in more than 90% of patients with Felty's syndrome.

TTT:

- **Pulsed corticosteroid and/or cyclophosphamide therapy** may be effective in raising neutrophils count,
- **G-CSF** to stimulate the production of granulocytes,
- **Splenectomy** (if failed to respond to medical tt).

NB: **Active RA** on methotrexate with **leukopenia** >>>? **Methotrexate-induced** or **Felty's syndrome (+ve ANA)**.

**EX:** Female 66 years old, long history of RA on methotrexate, she has worsening rheumatoid nodules, dry eyes, splenomegaly, pancytopenia TLC 3.5, Hb 9.5, PLT 100 >>> **Felty's syndrome** >>> 1<sup>st</sup> TTT is **pulse corticosteroid** (NOT hold methotrexate).



**Cyclophosphamide** causes **premature ovarian failure** and **infertility** in **both** men and women.

The risk increases with increasing doses of cyclophosphamide and is greater in **younger patients**.

Cyclophosphamide treatment does **not** lead to breast cancer, hyperthyroidism, ovarian cancer, or venous thromboembolism.

### Methotrexate

Methotrexate is an antimetabolite which **inhibits dihydrofolate reductase (DHFR enz)**, an enzyme essential for the synthesis of purines and pyrimidines.

Indications:

- Rheumatoid arthritis
- Psoriasis
- ALL acute lymphoblastic leukaemia

Adverse effects:

- **Hepatitis** and Liver cirrhosis
- **Myelosuppression**
- **Pneumonitis**
- **Pulmonary fibrosis**
- Mucositis

Pregnancy:

- Women should avoid pregnancy for at least 3 months after treatment has stopped.
- The BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment.

Men and women should avoid pregnancy for at least **3 months after** MTX ttt has stopped.

### Prescribing methotrexate:

- Methotrexate is a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use.
- Methotrexate is taken **weekly**, rather than daily.
- Dose started from 7.5 mg up to 20 mg per week.

- FBC, U&E and LFTs need to be regularly monitored.
- The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'.
- **Folic acid 5mg once daily** should be co-prescribed, taken more than 24 hours after methotrexate dose.
- Only one strength of methotrexate tablet should be prescribed (usually 2.5 mg).
- **Avoid** prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia.
- Methotrexate is recognised to be associated with pulmonary fibrosis. **Baseline pulmonary function tests (PFTs)** are recommended prior to starting therapy, and physicians are warned to be alert to increased shortness of breath.

**NB:** Methotrexate is a folic acid antagonist which can result in **multi-organ failure** in **overdose**.

**Folinic acid (Calcium folinate) (Leucovorin) IVI** is the **antidote** for the effect of methotrexate on the **haematopoietic system** and should be given **IV infusion as soon as possible, regardless** of the liver function tests, Dose: 75 mg in the first 12 hrs, and can then be followed by 6-12 mg every 4 hrs.

Blood transfusion may be required in exceptional circumstances.

Supportive measures by good hydration and urinary alkalinization may be used.

Standard dialysis is ineffective in removing methotrexate, although intermittent high flux dialysis may be of value.

**NB:** The current recommendation is that **CBC, U&Es and LFTs are checked at baseline** and then **two-weekly until the dose and monitoring is stable for 6 weeks**. These should then be checked **monthly** until the dose and disease is stable for a year. After this monitoring can be reduced to every two to three months if advised by a specialist.

The most appropriate time interval for **monitoring his full blood count (CBC)** according to current UK guidance would therefore be in **one month**.

Thereafter, monitoring is guided by clinical judgement. **If white cell count is less than 3.5, neutrophils less than 2 or platelets less than 150**, methotrexate should be **withheld** pending discussion with the specialist team.

An **MCV greater than 105 fL** warrants checking B12, folate and TSH and treating any abnormality. If these are normal, discuss with the specialist team.

**Liver function tests** should be **checked 3 monthly**. If there is an unexplained decrease in albumin, or AST/ALT twice the upper limit of normal, the specialist team should be informed.

**Urea, creatinine and electrolytes** should be **checked 6 monthly**. If the eGFR falls below 50 mL/minute, methotrexate should be withheld until the result be discussed with the specialist team.

In addition to this monitoring, **any clinical signs of toxicity should be monitored** for. If the patient develops rash, oral ulceration, sore throat, easy bruising or bleeding, shortness of breath, abdominal pain, nausea, vomiting, diarrhoea or jaundice, methotrexate should be withheld until discussed with the specialist team. **It should be documented in patient notes that this advice has been given.**

A sore throat or abnormal bruising should be investigated with an FBC, and methotrexate withheld until the results available.

In the setting of **acute infection, most DMARDs (except hydroxychloroquine)** should be **discontinued until** the infectious process has resolved.

So patient on **methotrexate** and develop **lower respiratory tract infection** with **normal** CXR, CBC, LFTs, U&E.

The most appropriate action is > **Stop methotrexate temporarily + Antibiotics (oral/IV).**

**Methotrexate-related lung toxicity:** a large spectrum of diseases ranging from **interstitial pneumonitis** to cough, pleuritic chest pain and SOB related to lung infiltration, associated with bilateral pleural effusions.

TTT: **Methotrexate withdrawal** and **replace** with anti-TNF or anti-CD20 antibody.

### **Sulfasalazine**

Current UK guidance suggests that during the first 3 months of treatment with sulfasalazine, **CBC** should be monitored **monthly** for **the first 3 months**.

Sulphasalazine should be withheld until discussion with the specialist team if:

- The white cell count is less than 3.5

- Neutrophils is less than 2, or
- Platelets are less than 150.

If mean corpuscular **volume (MCV) is more than 105 fl**, vitamin **B12, folate** and **TSH** should be checked and treated if found to be abnormal. If these are all normal it should be discussed with the specialist team.

If counts remain normal within the first 3 months, **CBC can be checked 3 monthly**.

Liver function tests (**LFTs**) should also be checked **monthly** for the first 3 months. If either AST or ALT are **more than twice the upper limit** of normal, sulfasalazine should be **withheld** until discussion with the specialist team.

If the LFTs remain normal for the first 3 months, monitoring can be decreased **to 3 monthly**.

If, following the first year, the dose has not been increased and blood results have been stable, the frequency of monitoring can be reduced to **every six months** for the second year of treatment. Thereafter monitoring is not required, although CBC and LFTs should be checked one month after any dose increase.

Side effects of sulfasalazine include **hypersensitivity**, **myelosuppression**, **macrocytosis**, and **azoospermia in males**.

There are numerous signs of sulfasalazine toxicity. Rash and oral ulceration should be asked about and, if severe, the drug should be withheld until specialist advice has been sought. Nausea, dizziness and headache can be common and sometimes necessitate dose reduction. If patients present with abnormal bruising or sore throat an urgent CBC should be done, and sulfasalazine withheld until results are available.

#### **Leflunomide (Arava® 20 mg tab)**

Leflunomide is associated with serious **hepatotoxicity**.

Increased aminotransferases are commonly seen in association with therapy occurring in 15-20% of cases (**less than a twofold rise**).

However, **more serious elevation (greater than threefold)** is seen in less than 5%.

Generally, most hepatic events occur within the first 6 months of use. It is recommended liver function tests (**LFTs**) be checked **monthly** for 6 months and, if stable, **2 monthly thereafter**.

If AST or ALT is **between 2 and 3 times the upper limit** of normal, and the leflunomide dose is more than 10 mg daily, the dose should be **reduced to 10 mg**

and **LFTs rechecked weekly** until normalised. If the ALT and AST are returning to normal, the patient should be left on 10 mg per day. If the LFTs remain elevated, leflunomide should be stopped and discussed with the specialist team.

If the AST or ALT is **more than 3 times the upper limit** of normal, the **LFTs should be rechecked within 72 hours**. If they **remain** more than 3 times the reference range, leflunomide should be **stopped** and **washout** considered (cholestyramine and activated charcoal).

It is important to note that the **half-life of leflunomide is usually 2 weeks** (mean 1-4) therefore if a rapid response is required, washout should be considered.

Current UK guidance also recommends frequent monitoring for patients on leflunomide. Full blood count (**CBC**) should be checked **monthly** for six months and, if stable, two monthly thereafter.

White cell count less than 3.5, neutrophils less than 2 or platelets less than 150 should be discussed with the specialist team, and leflunomide withheld until this has taken place.

Monitoring should be continued at least monthly in the long term if leflunomide is co-prescribed with any other immunosuppressant or potentially hepatotoxic agent.

In addition, **signs of leflunomide toxicity** should be monitored. If the patient develops a rash or itch dose reduction should be considered, with or without the addition of antihistamines. If severe, leflunomide should be stopped and washout considered.

Hair loss, headaches and gastrointestinal upset may also warrant dose reduction or washout.

A blood pressure of greater than 140/90 mmHg should be treated as per NICE guidelines. If it remains elevated, stop leflunomide and consider washout.

Weight should be monitored, and a weight loss of greater than 10% should be identified. If no other cause can be found, consider dose reduction or washout.

If there is increasing shortness of breath, pneumonitis should be considered and leflunomide should be stopped.

**Leflunomide reduces sperm count.** ☹

### Azathioprine (Imuran)

Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that **inhibits purine synthesis** (inhibits DNA synthesis).

A thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity.

**Azathioprine** - check **thiopurine methyltransferase deficiency (TPMT)** before treatment

Thiopurine methyltransferase (TPMT) deficiency is present in about 1 in 300 people and predisposes to azathioprine related pancytopenia.

The enzyme activity of TPMT is under the control of a genetic polymorphism.

**90%** of the population have normal or high enzyme activity, that is, are homozygous for the wild-type allele.

**10%** of the population have intermediate levels of TPMT activity, that is, one wild-type and one variant allele.

**One in 300** people have no functional enzyme activity.

Adverse effects include:

- Bone marrow depression >>> Pancytopenia
- Hepatotoxicity
- Pancreatitis
- Nausea/vomiting

A significant interaction may occur with **allopurinol** and hence lower doses of azathioprine should be used (so you may give only 25% of the usual dose of azathioprine).

The prodrug azathioprine is metabolised to its active compound 6-mercaptopurine (6-MP). 6-MP undergoes catabolic oxidation to 6-thiouric acid by xanthine oxidase.

Allopurinol has a peak onset of action of one to two weeks and works by inhibiting xanthine oxidase.

Co-administration of these drugs (**Imuran + Allopurinol**) may lead to **accumulation of 6-MP (6-MP toxicity)** and increases the **risk of myelosuppression (aplastic anaemia)**. ☹

The newer xanthine oxidase inhibitor, Febuxostat, can also result in the same problem and is also contraindicated.

Febuxostat is a **non-purine, selective xanthine oxidase inhibitor** unlike allopurinol, which is a purine analogue inhibitor of xanthine oxidase.

Current guidelines from the British Association of Dermatologists and the British National Formulary (BNF) suggest **monitoring CBC, LFTs and U&E every 3 months** once patients are established and stable on azathioprine treatment.

### **Hydroxychloroquine**

Hydroxychloroquine ocular toxicity includes:

- 1) Keratopathy
- 2) Ciliary body involvement
- 3) Lens opacities (**Lenticular deposits**)
- 4) **Retinopathy.**

Retinopathy is the major concern; the others are more common but benign.

The incidence of **true hydroxychloroquine retinopathy** is exceedingly **low**. Risk factors include:

- Daily dosage of hydroxychloroquine
- Cumulative dosage
- Duration of treatment
- Coexisting renal or liver disease
- Patient age, and
- Concomitant retinal disease.

Patients usually complain of difficulty in reading, decreased vision, missing central vision, glare, blurred vision, light flashes, and metamorphopsia. They can also be asymptomatic.

Most patients with advanced retinopathy have a **bull's eye** (also known as target, as in darts) fundoscopic appearance. All patients have field defects including **para-central, peri-central, and central and peripheral field loss**.

Regular screening may be necessary to detect reversible premaculopathy.

Cessation of the drug is the only effective management of the toxicity.

## In Pregnancy

In Pregnancy:

- **Methotrexate (teratogenic) and NSAIDs (1<sup>st</sup> trimester, risk of abortion) so they are absolutely contraindicated.**
- Prednisolone, Sulfasalazine and hydroxychloroquine are safe in pregnancy if these are necessary for treatment of the mother's disease.
- Sulfasalazine can be safely used prior to and during all stages of pregnancy, it is compatible with breast feeding, although should be advised with cautions because of the rare possibility that the mother is a slow acylator.
- Azathioprine can be used in pregnancy if Sulfasalazine and hydroxychloroquine are not controlling.
- Prednisolone and hydroxychloroquine may be taken whilst breast-feeding.
- Azathioprine, cyclophosphamide, methotrexate and cyclosporine are contraindicated in breast-feeding mothers.

**Azathioprine** can be used during pregnancy **if the benefits outweigh the risks**. Azathioprine can be continued at **the same dose**.

No apparent congenital malformations are known with doses up to 2mg/kg/day.

**During pregnancy >>> continue current dose of azathioprine and add folic acid.**

Breast feeding is not recommended with azathioprine.

**Corticosteroids**, the main alternative to azathioprine, are considered **relatively safe** in pregnancy when used in **low dose < 20 mg daily**.

However they may increase the **maternal risk** of HTN, oedema, gestational diabetes, osteoporosis, premature rupture of membranes (PROM), small-for-gestational-age babies (SGA), and increase in risk of cleft palate in foetus of first trimester.

The **lowest possible steroid dose** needed to control activity should be used in pregnancy if the choice is to follow this ttt option.

The routine use of **oral calcium and Vit D** is recommended.

**Stress doses of steroids** should be used **during labour and delivery** if the mother received steroids (even low dose) for more than 2-3 weeks during pregnancy, and the **neonate** should be **monitored** for evidence of adrenal insufficiency and infection.



## Sjögren's syndrome

- Sjögren's syndrome is an autoimmune disorder affecting exocrine glands resulting in dry mucosal surfaces.
- It may be either:
  - Primary Sjögren's syndrome (PSS) or
  - Secondary to RA, SLE or other connective tissue disorders, where it usually develops around 10 years after the initial onset.
- Sjögren's syndrome is much more common in **females** (ratio 9:1).
- There is a marked increased risk of lymphoid malignancy (NHL) (40-60 folds).

### Features:

- Dry eyes: keratoconjunctivitis sicca
- Dry skin.
- Dry mouth
- Dry vagina
- Arthralgia
- Raynaud's, myalgia
- Sensory polyneuropathy
- Renal tubular acidosis (usually subclinical)
- Plasma cell infiltration of salivary and lacrimal glands: Parotid swelling.

### Investigation:

- **RF** positive in nearly **100%** of patients
- **ANA** positive in **70%**
- **Anti-Ro** (SSA) antibodies in **70%** of patients with PSS
- **Anti-La** (SSB) antibodies in 30% of patients with PSS
- **Hypergammaglobulinaemia (↑ IgG)** in **80%**
- **Low C4**
- **Schirmer's test**: filter paper near conjunctival sac to measure tear formation (wetting of less than 5 mm in 5 minutes indicates defective tear production).
- **Rose Bengal staining of the eyes** commonly shows punctuate or filamentary keratitis.
- Histology: focal lymphocytic infiltration → ↑ **risk of lymphoid malignancy**

In RA, RF is positive in 80% of patients, whereas in Sjögren's syndrome and cryoglobulinaemia, it is prevalent in up to 90% of cases.

### Management:

- Artificial tears.
- Saliva replacement solution
- Vaginal lubricant.
- Pilocarpine may stimulate saliva production.

## Seronegative spondyloarthropathies

### Common features:

- Associated with HLA-B27
- **Rheumatoid factor negative** - hence 'seronegative'
- Peripheral arthritis, usually asymmetrical
- Sacroiliitis
- Enthesopathy: e.g. Achilles tendonitis, plantar fasciitis
- Extra-articular manifestations: uveitis, pulmonary fibrosis (upper zone), amyloidosis, aortic regurgitation

### Spondyloarthropathies:

- 1) Ankylosing spondylitis
- 2) Psoriatic arthritis
- 3) Reiter's syndrome (including reactive arthritis)
- 4) Enteropathic arthritis (associated with IBD)

## Ankylosing spondylitis (AS)

- Ankylosing spondylitis is a **HLA-B27** associated spondyloarthropathy.
- It typically presents in males (sex ratio 5:1) aged 20-30 years old.
- It has polygenic inheritance

### Features:

- Typically a young man who presents with **chronic lower back pain radiating to his buttocks**, and **stiffness** of insidious onset.
- **Stiffness** is usually **worse** in the **morning** more than 30 minutes and **worse** after periods of inactivity and **improves** with exercise.
- The patient may experience **pain** at night (waking in the second half of the night) which improves on getting up.
- Peripheral arthritis (25%, more common if female)
- Muscular strain is the commonest cause of back pain in general practice but **chronic pain for more than 3 months** may indicate AS and should be investigated.

The commonest subtype HLA associations are **HLA B\*2705** (Caucasians), **B\*2704** (Chinese, Japanese) and **B\*2702** (Mediterranean).

The B\*2706 subtype is weakly associated and commonly found in normal South East Asian individuals.

### Clinical examination:

- Reduced lateral flexion
- Reduced forward flexion - Schober's test - a line is drawn 10 cm above and 5 cm below the back dimples (dimples of Venus). The distance between the two

lines should increase by more than 5 cm when the patient bends as far forward as possible

- Reduced chest expansion
- Sacroiliac joint tenderness
- **Later (In the advanced stages of AS):** loss of lumbar lordosis, buttock atrophy and an accentuated thoracic kyphosis.

Other features - the '**A**'s:

- Apical fibrosis
- Anterior uveitis
- Aortic regurgitation
- Achilles tendonitis
- AV node block
- Amyloidosis
- And cauda equina syndrome
- Peripheral arthritis (25%, more common if female)

#### **Investigation:**

- Inflammatory markers (ESR, CRP) are typically raised although normal levels do not exclude ankylosing spondylitis.
- HLA-B27:
  - It is not essential for the diagnosis of AS.
  - It not used as a screening test for AS.
  - It is of little use in making the diagnosis and as it is positive in:
    - **90%** of patients with ankylosing spondylitis
    - 75% of patient with Reiter's syndrome.
    - 10% of normal patients
  - Its sensitivity and specificity depend on the **racial and ethnic background** of the patient.
  - Acute anterior uveitis is more common in B27 positive than negative patients.
- **Plain x-ray of the sacroiliac joints** is the most useful investigation in establishing the **diagnosis** and **monitoring**, but changes may not be seen for many years after the onset of symptoms. Radiographs may be normal early in disease, later changes include:
  - Sacroilitis: sub-chondral erosions, sclerosis
  - **Squaring** of lumbar vertebrae
  - 'Bamboo spine' (late & uncommon)
  - Syndesmophytes: due to ossification of outer fibers of annulus fibrosus
  - Chest x-ray: apical fibrosis

- Spirometry may show a restrictive defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

**Current British Society for Rheumatology** recommendations state that **the modified New York criteria** should be used to **diagnose ankylosing spondylitis**:

**Clinical Criteria:**

- Low back pain, present for more than 3 months, improved by exercise but not relieved by rest.
- Limitation of lumbar spine motion in both the sagittal and frontal planes.
- Limitation of chest expansion relative to normal values for age and sex.

**Radiological Criteria:**

- Sacroiliitis on **x ray**.

**Diagnose:**

- Definite AS if the radiological criterion is present plus at least one clinical criterion.
- Probable AS if 3 clinical criteria are present alone or if the radiological criterion is present but no clinical criteria are present.

Both **HLA-B27** and **sacroiliitis on MRI** play a major role in the recently proposed Assessment of Spondyloarthritis International Society (ASAS) diagnostic algorithm. This may replace the modified New York criteria in the future.

**Management:**

The following is partly based on the 2010 EULAR guidelines (European League Against Rheumatism):

The **best initial** therapy for **AS** is **NSAIDs** and **physiotherapy**.

- **NSAIDs** are the first-line treatment.
- **Physiotherapy**
- Encourage regular exercise such as swimming
- If symptoms are not controlled additional analgesics (for example, amitriptyline).
- Corticosteroid injections or oral corticosteroids can be used.
- The DMARDs which are used to treat RA (such as sulphasalazine) are only really useful if there is peripheral joint involvement as it doesn't improve spinal mobility.

- The 2010 EULAR guidelines suggest: '**Anti-TNF** therapy should be given to patients with persistently high disease activity despite conventional treatments' (severe ankylosing spondylitis which has failed to respond to NSAIDs.)
- Research is ongoing to see whether anti-TNF therapies such as etanercept and adalimumab should be used earlier in the course of the disease.

### **Psoriatic arthropathy**

- Psoriatic arthropathy **correlates poorly with cutaneous psoriasis** and **often precedes** the development of skin lesions. (عبادی قبل عبد الجلیل)
- Around **10%** of patients with skin lesions develop an arthropathy with males and females being **equally** affected.
- The condition can present with or without the associated psoriatic skin lesions or only with **nail malformations** (**onycholysis**, **transverse ridging** and **pitting** of fingernails).
- If no obvious skin lesions are visible, the clinician should look for psoriasis in **hidden sites** such as the scalp, intergluteal cleft and umbilicus.
- **Extra-articular features** of the condition include **flexor tendon synovitis** and **uveitis**.
- It is associated with an increased frequency of **HLB-B7** and **HLA-B27**.

**There are 5 classic presentations (Types) of psoriasis:** based on the pattern of joint involvement.

- 1) **Rheumatoid-like polyarthritis:**
  - **Symmetrical polyarthritis:** (30-40%, **most common type**):
  - It affects wrists, hands, feet and ankles.
  - The **distal interphalangeal joints (DIP)** are more commonly affected than the metacarpophalangeal joints.
- 2) Asymmetrical oligoarthritis: typically affects hands and feet (20-30%)
- 3) **DIP** joint disease (10%)
- 4) Spondylitic pattern: Sacroilitis
- 5) Arthritis mutilans (severe deformity fingers/hand, 'telescoping fingers')

Management:

- **Treat as rheumatoid arthritis, but better prognosis** 😊
- **DMARD** (e.g., methotrexate, leflunomide, sulfasalazine): to prevent joint damage from proliferative/ erosive changes in psoriatic arthritis.
- In the UK, **anti-TNF agents** are used for the ttt of psoriatic arthritis **only if** the patient fails to respond to an adequate **trial of two DMARDs**.
- **Hydroxychloroquine** has been shown to **exacerbate psoriatic skin lesions** in certain situations, and is therefore used with caution if at all.

- In patients with cutaneous psoriasis, systemic corticosteroids predispose to pustular psoriasis, and may result in a flare of skin psoriasis when they are stopped.
- Ustekinumab: It is a fully human IgG1k monoclonal antibody to interleukin (IL) 12/23. It is not an anti-TNF agent so no neutropenia or reactivation of TB. Adverse effect is: dental infection.

### **Still's disease in adults (= Adult onset Still's disease (AOSD))**

It is a **rare** systemic inflammatory disease.

It typically affects **15-35 year olds**.

Etiology is not clearly understood, but it is likely triggered by an infectious agent in a genetically predisposed host.

**Diagnosis is clinical**, and should include **exclusion** of infectious disease, neoplasms and other autoimmune disease.

Systemic features may precede the onset of arthritis.

#### **Features:**

- Polyarthralgia (wrists, knees, ankles, elbows and metacarpophalangeal joints)
- There is often an accompanying sore throat and myalgia.
- Evanescent salmon-colored non-pruritic macular or macular-papular **rash**: **90%** of patients and is often seen **only when the patient is febrile** and is easily missed.
- Swinging pyrexia (**intermittent fever**): occurs once or twice daily and is described as quotidian or diquotidian returning to 37°C or below between episodes.
- Serositis: pleurisy with pleuritic chest pain, pericardial rub.
- Reticuloendothelial activation: Lymphadenopathy & Hepatosplenomegaly
- ↑TLC, ↑PLT
- ↑ESR, ↑CRP, ↑Ferritin
- RF, ANA, and anti-DNA: Negative (Autoimmune Abs are negative).
- **In between** the febrile episodes the patient feels rather **well**.

Management:

- **NSAIDs.**
- Steroids.
- Methotrexate.

The prognosis is better than for adult RA.

**EX:** A 25-year-old student presents to the casualty department with a **systemic illness**. She appears **unwell**, with a **swinging fever**, **3 kg weight loss** over 2 months, **generalised myalgia**, **polyarthralgia** affecting wrists, knees, ankles, elbows and metatarsophalangeal joints, and a **sore throat**, **pleurisy**, **pericardial rub**, **pericardial effusion**, **hepatomegaly**, **enlarged anterior cervical LN**.

Investigations demonstrate normochromic normocytic **anaemia 9.8 g/l**, TLC 20,000, PLT 500,000, **ESR 81 mm**, **CRP 31 g/l**, serum **ferritin 1756 mg/dl**, **RF negative**, **ANA negative**, ASO titre <200iu.

The most likely diagnosis is >>>**AOSD**

**DD** Polymyositis is an inflammatory condition which typically presents with relatively painless, progressive, proximal muscle weakness.

**EX: Juvenile idiopathic arthritis (still's disease):**

Normally occurs in **younger** children, it may occasionally present in **adolescents** and young adults.

Up to 25% of cases have **+ve ANA**.

**Microcytic anaemia** which tends to be resistant to iron replacement.

**Pericarditis** is often found.

TTT: NSAIDS, corticosteroids, methotrexate and anti-TNF biologicals.

### Extractable nuclear antigens

Overview:

- specific nuclear antigens
- usually associated with being ANA positive

Examples:

- **Anti-Ro**: Sjogren's syndrome, SLE, congenital heart block
- **Anti-La**: Sjogren's syndrome
- **Anti-Jo 1**: polymyositis (more than Dermatomyositis)
- **Anti-centromere**: limited cutaneous systemic sclerosis
- **Anti-scl-70 (Anti-topoisomerase I)**: diffuse cutaneous systemic sclerosis

**Systemic lupus erythematosus (SLE)**

SLE is a heterogeneous multisystem autoimmune inflammatory disease, in which ANA occur. Its presentation and course are highly variable, ranging from indolent to fulminant.

**Epidemiology:**

- Much more common in females (**F:M = 9:1**)
- More common in Afro-Caribbeans\* and Asian communities
- Onset is usually **20-40 years**
- Incidence has risen substantially during the past 50 years (3 fold using American College of Rheumatology criteria)

**Pathophysiology:**

- Autoimmune disease
- Associated with **HLA B8, DR2, DR3**
- Thought to be caused by immune system dysregulation leading to immune complex formation
- Immune complex deposition can affect any organ including the skin, joints, kidneys and brain

\*It is said the incidence in black Africans is much lower than in black Americans - the reasons for this are unclear

**Immunology:**

- **ANA** is highly sensitive and positive in over 95%, but not specific.
- **Anti-dsDNA: HIGHLY specific (100%)**, but less sensitive (70%).
- **Anti-Smith: MOST specific (100%)**, sensitivity (30%)
- also: **anti-U1 RNP**, **SS-A (anti-Ro)** and **SS-B (anti-La)**
- Low levels of **C3** and **C4** (C4a and C4b)
- 20% are rheumatoid factor positive

**SLE: ANA is 99% sensitive - anti-dsDNA & anti-Sm are 99% specific**

**Anti-dsDNA antibodies are highly specific (100%) for diagnosis of SLE.**

Its level correlates with lupus **activity**.

However, they are **neither necessary, nor sufficient** in themselves for the diagnosis of SLE.

At any one time **only 50% patients with SLE have the anti-dsDNA antibody**, while only 70% patients with SLE develop anti-dsDNA antibodies at any one time during the course of their illness.



**Monitoring:**

- 1) **ESR**: during active disease the CRP is characteristically normal - a raised CRP may indicate underlying infection. (Very high CRP is unusual with SLE).
- 2) Complement levels (**C3, C4**) are low during active disease (formation of complexes leads to consumption of complement) (↓C4 is early marker for disease activity) (although congenital C4 deficiency is itself a predisposing factor for SLE development so these tests must be interpreted with caution).
- 3) **Anti-dsDNA titres** can be used for **disease activity monitoring** and often levels will rise just before a flare of disease. (But it is not present in all patients).

**Early markers of SLE disease activity:**

- 1) **High ESR.**
- 2) **Low C4.**
- 3) **High Anti-dsDNA titres.**
- 4) **Falling Hb, TLC & PLT.**
- 5) **Falling albumin.**
- 6) Rising immunoglobulins (e.g. **high IgG**).

Although not mutually exclusive, different **ANA immunofluorescence patterns** suggest different diseases:

- **Anti-centromere** pattern: limited cutaneous systemic sclerosis
- **Cytoplasmic** pattern: Sjögren's syndrome, anti-synthetase syndrome
- **Nucleolar** pattern: diffuse cutaneous systemic sclerosis, polymyositis
- **Speckled** pattern: RA, SLE, Sjogren syndrome, systemic sclerosis, polymyositis, mixed connective tissue disease.
- **Homogenous (diffuse)** : SLE, mixed connective tissue disease

**Features:****General features:**

- Fatigue
- **Fever**
- Mouth ulcers
- Lymphadenopathy

**Skin:**

- **Malar (butterfly) rash: spares nasolabial folds**
- Discoid rash: scaly, erythematous, well demarcated rash in sun-exposed areas. Lesions may progress to become pigmented and hyperkeratotic before becoming atrophic.

- Photosensitivity
- Raynaud's phenomenon
- Livedo reticularis
- Non-scarring alopecia

Musculoskeletal:

- **Arthralgia**
- Non-erosive arthritis

Cardiovascular:

- Myocarditis

Respiratory:

- **Pleurisy & pleural effusions:** It is the **most common** manifestation of **SLE related lung disease** in up to **60%** of cases with reporting pleuritic chest pain ± concomitant pleural effusion >>> ttt: antibiotic (Amoxicillin).
- Chronic interstitial pneumonitis (CIP): in 15%.
- Fibrosing alveolitis

Renal:

- Proteinuria
- Glomerulonephritis (**diffuse proliferative class 4 IV glomerulonephritis** is the most common type)

Neuropsychiatric lupus:

- Anxiety and depression
- Psychosis
- Seizures
- Amenorrhea

The malar rash, arthralgia, lethargy and history of mental health >> points towards a diagnosis of SLE.

Remember that the CRP (in contrast to the ESR) is typically normal in SLE.

### SLE and pregnancy

- Unlike many autoimmune diseases, systemic lupus erythematosus (SLE) often becomes **worse** during **pregnancy** and the **puerperium**.
- Risk of maternal autoantibodies crossing placenta
- Leads to condition termed neonatal lupus erythematosus
- Neonatal lupus presents as erythematous macular rash on face or trunk, which may be photosensitive. It is a transient self-resolving illness due to passively transmitted maternal antibodies.

- Neonatal complications include **congenital complete heart block (CHB)**.
- Strongly associated with **anti-Ro (SSA)** antibodies.
- **Risk of pre-eclampsia** is increased in SLE. It may be difficult to differentiate between pre-eclampsia and renal flare of SLE, and both may coexist. Differentiating features include raised anti-dsDNA antibody, decreased levels (C3 and C4) and response to steroids in the case of renal flare.

SLE >>> antibody associated with congenital heart block of baby is >>> **Anti-Ro**

**Complications of pregnancy in Sjogren's syndrome:**

**Anti-Ro**, and **anti-La** antibodies cross the placenta, and cause fetal AV nodal conduction defect, which may progress to complete heart block (**CHB**). This may be complicated by congestive cardiac failure (**CCF**), and **hydrops fetalis**.

**EX:** A 35-year-old woman who was 2 months postpartum presented with a 4 weeks history of **joint pain**, **facial rash** and **fever**. **ESR of 40 mm/hour (0-20)**.

The most likely diagnosis is >>> **SLE**.

The triad of fever, arthralgia and rash in a woman of childbearing age should suggest the diagnosis of SLE.

**Diffuse Infiltrative lymphocytic syndrome (DILS)** can present like **Sjogren's** syndrome with **parotid gland enlargement** and **sicca** symptoms (dry eye & mouth). Extra glandular manifestations are common and it is rare for the patient to have positive autoantibodies unlike Sjogren's syndrome (i.e. **NEGATIVE** RF and ANA). The weakness is due to a peripheral motor neuropathy. Aseptic meningitis and cranial nerve palsies can also occur. Lymphocytic interstitial pneumonitis is the most serious complication of DILS.

**Drug-induced lupus (DIL)**

In drug-induced lupus not all the typical features of SLE are seen, with renal and nervous system involvement being unusual.

It usually resolves on stopping the drug.

Symptoms are said to appear some 3 weeks to 2 years after onset of therapy.

Patients with the HLA-DR3 antigen appear to be particularly at risk of developing drug-induced lupus.

Glomerulonephritis is unusual in drug-induced lupus

Features:

- Arthralgia
- Myalgia
- Malaise
- Skin (e.g. malar rash) on face and upper chest in 25% of sufferers.
- Raynaud's phenomenon is seen in around 25%.
- Pulmonary involvement (e.g. pleurisy) are common
- ANA positive in 100%, but dsDNA negative
- Anti-histone antibodies are found in 95%
- Anti-Ro, anti-Smith positive in around 5%
- Hypergammaglobulinaemia ( $\uparrow$  IgG)
- Normal C3 and C4.

A strongly positive ANA is a risk factor for developing drug-induced lupus, but a negative ANA would not exclude the diagnosis.

**Classically, drug-induced lupus erythematosus is characterised by**

- 1) **Systemic disease** with a **lower incidence of nephritis**
- 2) **Lack of cutaneous** involvement and
- 3) The presence of **ant histone antibodies**.

There are features which distinguish ***drug-induced lupus*** from idiopathic SLE:

- 1) **Males and females are equally affected** in drug-induced lupus, whereas idiopathic SLE affects females nine times more frequently.
- 2) **Caucasians** are affected by drug-induced lupus more commonly than Afro-Caribbeans, whereas the inverse is true of idiopathic SLE.
- 3) In addition, the **age** of onset is typically **older** in drug-induced lupus at **50-70** years, but this depends on the age at drug exposure.
- 4) **Fever, arthralgia, serositis** and **ANA** occur at least as frequently in drug-induced lupus as idiopathic SLE.
- 5) Haematological, renal and CNS involvement, and ds-DNA Ab are **rare**.

Most common causes:

- Hydralazine
- Procainamide

Less common causes:

- Phenytoin
- Valproate (Depakin)
- Carbamazepine
- Penicillamine

- Isoniazid
- **Sulfasalazine**
- **Minocycline** (ttt of acne)
- Chlorpromazine
- Methyldopa
- Beta blocker
- **ACEI (captopril)**
- **Statins**
- PTU
- Interferons
- Anti- TNF alpha agents (infliximab and etanercept).

Treatment:

- **Stopping** of the offending drugs.
- Low dose corticosteroids can be used.

**EX:** 16-year-old girl presents with a **3 month history of polyarthralgia** and **marked early morning stiffness**.

Her symptoms respond well to diclofenac but she is becoming increasingly concerned about her symptoms which appear to be **progressing**. She is otherwise well apart from a history of **acne** which is well controlled on **minocycline**. Her mother has severe rheumatoid arthritis.

**Lab:** ESR= 50, CRP=100, RF=Negative, ANA=Strongly Positive, Anti-dsDNA=Negative, IgG=25↑ (N <15 g/L).

The most likely cause is >>> **Drug-induced SLE >>> TTT: Stop minocycline.**

**EX:** A 22-year-old woman is on sulfasalazine (2 gm/day) for three 3 for mild inflammatory arthritis. Over the last 2 wks. She has developed worsening arthralgia, swollen MCP joints, fatigue and low grade fever, oral ulcers, and widespread papular erythematous rash >>> **Drug-induced SLE, TTT Stop sulfasalazine.**

The **time** taken for symptoms to **resolve** after stopping minocycline is **highly variable, from a few days to 2 years**.

Typically, no further treatment is required but there are situations where corticosteroids or DMARDs are required to aid resolution.

**Discoid lupus erythematosus**

- Discoid lupus erythematosus is a benign disorder generally seen more commonly in **younger African-Caribbean females**.
- It is a variant of SLE, in which skin involvement is the main feature.
- It very rarely progresses to SLE (in less than 5% of cases).
- Usually there is negative ANA and anti-DNA.
- It is characterised by **follicular keratin plugs** and is thought to be autoimmune in aetiology.
- Lesions are discrete plaques, often erythematous, covered by scales that **extend into dilated hair follicles**. These lesions most typically occur on the face, scalp, in the pinnae, behind the ears and on the neck. They can exist in areas not exposed to the sun.
- The lesions can progress, with active indurated erythema at the periphery.
- **Central atrophic scarring** is characteristic.
- Diagnosis is made by lesion biopsy.

**Features:**

- Erythematous, raised rash, sometimes scaly
- May be photosensitive
- More common on face, neck, ears and scalp
- Lesions heal with atrophy, scarring (may cause **scarring alopecia**), and pigmentation

**Management:**

- Topical steroid cream
- Oral antimalarials may be used second-line e.g. hydroxychloroquine
- Avoid sun exposure

**NB: Skin disease** may occur as part of SLE, or be present as cutaneous lupus erythematosus (frequently without any systemic disease), and with variable chance of progression to SLE.

- Discoid lupus erythematosus (**DLE**)
- Subacute cutaneous lupus erythematosus (**SACLE**)
- Acute cutaneous lupus erythematosus (**ACLE**)

In SACLE there is **ANA positive** in **60%** patients. However, only 10-15% progress to SLE with moderate disease activity. **80%** of patients are **anti-Ro antibody positive**.

**Antiphospholipid syndrome (Hughes' syndrome)**

It is an acquired disorder characterised by a predisposition to both venous and arterial thrombosis, recurrent fetal loss and thrombocytopenia. It may occur as a primary disorder or secondary to other conditions, most commonly SLE.

It is **the most common cause** of **recurrent 1st trimester spontaneous miscarriage**.

It is thought to be the cause of complications in around 45/100,000 pregnancies.

Antiphospholipid antibodies (aPL) are present in **15% of women with recurrent miscarriage**, but in comparison, the prevalence of aPL in women with a low risk obstetric history is less than 2%.

A key point for the exam is to appreciate that Antiphospholipid syndrome causes a **paradoxical rise in the APTT**. This is due to an ex-vivo reaction of the lupus anticoagulant autoantibodies with phospholipids involved in the coagulation cascade

APLS >>> paradoxical ↑ **APTT** with ↓ **PLT**

APLS: **Prolonged PTT** in the presence of **normal PT**

Features:

- Recurrent fetal loss (3 unexplained mid-trimester miscarriage).
- Venous/arterial thrombosis: DVT, PE, (BRVO Branch Retinal Vein Occlusion causing sudden blindness)
- Thrombocytopenia
- Prolonged APTT
- Livedo reticularis
- Chorea
- Libman-sacks endocarditis
- Other features: pre-eclampsia, pulmonary hypertension

It is associated with arterial and venous thrombosis and has a predilection for **the adrenal veins** causing **adrenal infarction** with consequent **hypoadrenalism**.

APLS may be a **primary** diagnosis or may co-exist with SLE (secondary).

Associations other than SLE:

- Other autoimmune disorders: SLE, RA & Sjogren's.
- Lymphoproliferative disorders
- Phenothiazines (rare)

**Positive anticardiolipin antibodies** or a **lupus anticoagulant** are detected on 2 **separate** occasions, separated **by at least 6 weeks**.

In pregnancy: the following complications may occur:

- Recurrent miscarriage.
- IUGR
- Pre-eclampsia
- Placental abruption
- Pre-term delivery
- Venous thromboembolism

Management during pregnancy:

- Low-dose aspirin should be commenced once the pregnancy is confirmed on urine testing.
- LMWH once a fetal heart is seen on ultrasound. This is usually discontinued at 34 wks gestation.
- These interventions ↑ the live birth rate 7 folds.
- Others: Omission of smoking and OCPs.

Management - based on BCSH guidelines:

- **initial venous** thromboembolic events: evidence currently supports use of warfarin with a target INR of 2-3 for 6 months
- **recurrent venous** thromboembolic events: lifelong warfarin;
- **If occurred whilst taking warfarin** then increase target INR to 3-4
- **arterial** thrombosis should be treated with lifelong warfarin with target INR 2-3

### Churg-Strauss syndrome (CSS)

CSS is rare an ANCA associated small-medium vessel vasculitis.

The typical picture of a patient with CCS is asthma, allergic rhinitis, mild renal impairment, microscopic haematuria, raised eosinophilic count.

Asthma + Eosinophilia + Renal imp + Microscopic Haematuria + Nerve lesion >>> CSS
---

Features:

- 11) Asthma
- 12) Blood eosinophilia (e.g. > 10%)
- 13) Paranasal sinusitis



- 14) Non- fixed Pulmonary infiltrates (may be transient)
- 15) Histological proof of vasculitis with **extravascular eosinophils by vascular biopsy**.
- 16) Mononeuritis multiplex occurs 75% of patients (e.g. ulnar nerve palsy, foot drop) or polyneuropathy.
- 17) **pANCA** positive in 60%
- 18) Rarely, it can cause either an anterior or a posterior ischaemic optic neuropathy, which presents with visual loss.

A diagnosis of Churg-Strauss syndrome requires **4** of the following features:

- 7) Asthma
- 8) Eosinophilia greater than 10%
- 9) Paranasal sinus abnormality
- 10) Non-fixed pulmonary infiltrates visible on chest radiographs
- 11) Mononeuropathy or polyneuropathy and
- 12) Blood vessels biopsy with extravascular eosinophils.

TTT: Glucocorticoids, and immunosuppressant drugs (cyclophosphamide, azathioprine, MMF).

NB: Leukotriene receptor antagonists may precipitate the disease.

### Thrombangitis obliterans (Buerger's disease)

- It is a disease of small & medium sized arteries and veins resulting in inflammation and ulceration.
- No excessive atheroma.
- Does **not** involve the **coronary** arteries like atherosclerosis.
- Occurs mainly in cigarette smokers, it has not been documented in non-smoker.
- Patients present with symptoms of arterial ischemia (PVD).
- Migratory phlebitis in the superficial vein is present in 40% of cases.
- The disease progress proximally, resulting in **gangrene of the digits (fingers and toes)**.
- Negative RF, ANA, Anti-DNA.
- Diagnosis is usually clinical, however arteriogram is also of benefit and will show occlusion of distal arteries of the hands and feet.
- TTT is supportive and patients should stop smoking.

**Polyarteritis nodosa (PAN)**

Polyarteritis nodosa (PAN) is a systemic transmural **necrotising vasculitis** that usually affects **medium** sized **arteries** with necrotizing inflammation leading to **aneurysm** formation, aneurysmal rupture, **thrombosis** and subsequently organ **ischaemia and infarction**.

It is a **multisystem** disorder, most commonly in **middle-aged men**.

**Angiography** demonstrates microaneurysms in affected organs, and biopsy shows necrotising inflammation. (Polymorph nuclear infiltrate and a homogenous eosinophilic (so called **fibrinoid necrosis**) appearance to the necrosed vessel walls). **NO** granulomatous inflammation.

Signs and symptoms are primarily attributable to diffuse vascular inflammation and ischaemia of the affected organs

It most commonly affects skin, joints, peripheral nerves, the GIT and the kidney. The **lungs** are usually spared.

Virtually any organ with the exception of the lung can be affected, with **peripheral neuropathy** and symptoms from **osteoarticular**, **renal** artery, and **cardiac**, **neurological** and **gastrointestinal tract** involvement being the most frequent clinical manifestations.

The most common causes of death are from **renal** (HTN, renal failure) and **cardiac** (coronary arteritis, MI, pericarditis) involvement.

A typical presentation is with **fever**, night sweats, **weight loss**, skin ulceration and tender nodules, and **severe muscle and joint pains (polymyalgia and polyarthralgia)**.

PAN is more common in middle-aged men and is associated with hepatitis B infection.

PAN can be further classified into systemic vs limited (cutaneous) and idiopathic vs hepatitis B, and this is important due to differences in pathogenesis and therefore treatment and prognosis.

Features:

- Fever, malaise, poly-arthralgia, poly-myalgia.
- Weight loss > 5 Kg.
- **Hypertension** (DBP > 90 mmHg).
- Mononeuritis multiplex, sensorimotor polyneuropathy: e.g. foot drop.

- Testicular pain or tenderness (occasionally biopsy for diagnosis).
- Abdominal pain (dt mesenteric ischemia).
- Chest pain
- Skin lesions: purpura and Livedo reticularis.
- **Renal** involvement: haematuria, nephritic, renal failure.
- Positive ANA
- **pANCA** are found in around **only 20%** of patients with 'classic' PAN (i.e. is **not common**)
- Hepatitis **B** serology (HBsAg) positive in 30% of patients (? Homosexuals or IV drugs abuser).

**ACR criteria for diagnosis of PAN (must have 3 of the following):**

- 1) Weight loss > 5 Kg.
- 2) Skin lesions: purpura and Livedo reticularis.
- 3) Testicular pain or tenderness.
- 4) Myalgia, mono/polyneuropathy.
- 5) DBP > 90 mmHg.
- 6) Renal impairment.
- 7) HBV

**Diagnosis:**

By combination of clinical features plus renal or mesenteric angiography (microaneurysms).

**Treatment:**

- For idiopathic PAN is currently **corticosteroids** and **cyclophosphamide**,
- For hepatitis B related disease Plasmapheresis and antivirals should be used.
- **Azathioprine** can be used as maintenance therapy, and typically has fewer side effects than cyclophosphamide.

**Behcet's syndrome**

Behcet's syndrome is a complex multisystem vasculitis disorder associated with presumed autoimmune mediated inflammation of the arteries and veins. It is a vasculitis of unknown pathophysiology.

The precise aetiology has yet to be elucidated however.

The classic triad of symptoms are oral ulcers, genital ulcers and anterior uveitis.

Epidemiology:

- More common in the eastern Mediterranean (e.g. Turkey, Lebanese).
- More common in men (complicated gender distribution which varies according to country. Overall, Behcet's is considered to be more common and more severe in men).
- Tends to affect young adults (e.g. 20 - 40 years old)
- Associated in more than **60 %** with HLA B5 and MICA6 allele (more specifically HLA B51, a split antigen of HLA B5).
- Around 30% of patients have a positive family history.

Features:

- Classically: **1) oral ulcers 2) genital ulcers 3) anterior uveitis**
- Thrombophlebitis and DVT.
- Arthritis (asymmetrical, large joints like wrist and knee)
- Neurological involvement: severe occipital headache (e.g. aseptic meningitis).
- GIT: Abd pain, diarrhoea, colitis.
- Erythema nodosum.

Behcet's= Oral ulcer, Genital ulcer, Uveitis, Thrombophlebitis, Arthritis, Aseptic meningitis, Colitis.

**The International Study Group criteria for classification of Behçet's disease** requires:

The presence of **recurrent oral ulceration** (minor aphthous, major aphthous or herpetiform ulceration observed by physician or patient, which have recurred at least 3 times in a 12 month period), **and TWO** of the following:

- 1) **Recurrent genital ulceration**: aphthous ulceration or scarring, observed by physician or patient.
- 2) **Eye lesions**: branch retinal artery occlusion (BRAO), anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist.
- 3) **Skin lesions**: erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by the physician in post-adolescent patients not on corticosteroid treatment.
- 4) **Positive pathergy test**: read by physician at 24-48 hours.

Diagnosis:

- No definitive test
- Diagnosis based on clinical findings
- **Positive pathergy test** is the non-specific hyper-reactivity of the skin following minor trauma, and is specific to Behçet's disease. It involves

intra-dermal injection of skin with a 20-gauge needle under sterile conditions. It is considered positive if an erythematous sterile papule develops within 48 hours.

- **HLA B5** is associated with ocular disease; **HLA B12** is associated with recurrent oral ulcers.

TTT: Steroids + Azathioprine.

**NB:** Conjunctivitis is seen rarely and is much less common than anterior uveitis. Other ocular problems seen include scleritis, retinal vasculitis, iridocyclitis and chorioretinitis.

### ANCA

Anti-neutrophil cytoplasmic antibodies (ANCA) are **diagnostic markers for vasculitis**, although they may not be pathological.

There are two main types of anti-neutrophil cytoplasmic antibodies (ANCA) which are characterised by **neutrophil staining**: Cytoplasmic (cANCA) and perinuclear (pANCA)

These are largely synonymous with **PR3-ANCA (targeting peroxidase-3)** and **MPO-ANCA (targeting myeloperoxidase)**.

For the exam, remember:

- cANCA - Wegener's granulomatosis
- pANCA - Churg-Strauss syndrome + others (see below)

**cANCA (PR3-ANCA) = Wegener's**

**pANCA (MPO-ANCA) = Churg-Strauss + Microscopic polyangiitis & others**

#### cANCA: (PR3-ANCA)

- Most common target serine proteinase 3 (PR3).
- It correlates with **anti-proteinase 3** antibodies (**PR3**)
- Some correlation between cANCA levels and disease activity and the antibodies typically disappear when the disease is in remission.
- Wegener's granulomatosis, positive in > 90% (> more than 90% specificity)
- Microscopic polyangiitis, positive in 40%

**pANCA: (MPO-ANCA)**

- Most common target is **myeloperoxidase (MPO)** which is a neutrophil protein whose primary role is the generation of oxygen free radicals.
- Cannot use level of pANCA to monitor disease activity
- Associated with immune crescentic glomerulonephritis (positive in HCV 80% of patients)
- Churg-Strauss syndrome, positive in 60%
- Microscopic polyangiitis, positive in 50-75%
- Primary sclerosing cholangitis, positive in 60-80%
- Wegener's granulomatosis, positive in 25%

Other causes of positive ANCA (usually pANCA):

- Inflammatory bowel disease (**UC** 70%> Crohn's 20%)
- Connective tissue disorders: RA, SLE, Sjogren's
- Autoimmune hepatitis

**Chronic fatigue syndrome (CFS)**

Diagnosed after at least 4 months of disabling fatigue affecting mental and physical function more than 50% of the time in the absence of other disease which may explain symptoms.

Epidemiology:

- more common in females
- past psychiatric history has not been shown to be a risk factor

Fatigue is the central feature, other recognised features include:

- Sleep problems, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleep-wake cycle
- Muscle and/or joint pains
- Headaches
- Painful lymph nodes without enlargement
- Sore throat
- Cognitive dysfunction, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding
- Physical or mental exertion makes symptoms worse
- General malaise or 'flu-like' symptoms
- Dizziness
- Nausea
- Palpitations

Investigation:

- NICE guidelines suggest carrying out a large number of screening blood tests to exclude other pathology e.g. FBC, U&E, LFT, glucose, TFT, ESR, CRP, calcium, CK, ferritin, coeliac screening and also urinalysis

Management:

- Cognitive behaviour therapy - very effective, number needed to treat = 2
- Graded exercise therapy - a formal supervised program, not advice to go to the gym
- 'Pacing' - organising activities to avoid tiring
- Low-dose amitriptyline may be useful for poor sleep
- Referral to a pain management clinic if pain is a predominant feature

Better prognosis in children

### **Fibromyalgia (FM)**

Fibromyalgia is a syndrome characterised by widespread pain throughout the body with tender points at specific anatomical sites.

The cause of fibromyalgia is unknown but may involve hyperexcitability within the spinal cord or brainstem, altered pain perception and somatisation.

Epidemiology:

- It occurs in between 1-2% of the general population.
- Women are 10 times more likely to be affected
- Typically presents between 30-50 years old

Features:

- Pain: at multiple site especially around the shoulders and neck , sometimes **'pain all over'**
- Lethargy, Morning fatigue
- Patients often look unwell, and may appear depressed and anxious.
- Sleep disturbance, headaches, dizziness are common
- Diarrhoea and constipation in 50% , often associated with abdominal bloating
- Urinary frequency.
- Normal all investigations: CBC, ESR, CRP, U&E, LFTs, Thyroid, and autoimmune screen.

Diagnosis is clinical and sometimes refers to the American College of Rheumatology classification criteria which list 9 pairs of tender points on the body. If a patient is **tender in at least 11 of these 18 points** it makes a diagnosis of fibromyalgia more likely.

The management of fibromyalgia is often difficult and needs to be tailored to the individual patient.

A psychosocial and multidisciplinary approach is helpful. Unfortunately there is currently a paucity of evidence and guidelines to guide practice. The following is partly based on consensus guidelines from the European League against Rheumatism (EULAR) published in 2007.

- Explanation
- Exercise programme
- Cognitive behavioural therapy
- Analgesia
- Anti-depressants: amitriptyline

**NB:** No role of Trigger point injections

### Temporal arteritis (TA) = (Giant cell arteritis) (GCA)

Temporal arteritis is **large vessel vasculitis** which **overlaps with polymyalgia rheumatica (PMR)**.

GCA affects large and medium sized arteries, with a predilection for the external carotid, ciliary and retinal arteries.

Endovascular damage and cytokine-mediated inflammation causes local ischaemia.

Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.

Giant cell arteritis is a clinical emergency and should be treated without delay. It is not acceptable to give no treatment.

**20%** of patients develop **loss of vision**, which can be prevented with timely recognition and treatment. Visual loss typically occurs early in the course of disease and, once established, rarely improves.

As soon as the diagnosis is suspected, **high dose corticosteroids** should be given.

**Old man, Intermittent headache, lethargy with ↑ESR >>>> Temporal arteritis**



**Features:**

- Typically patient > 60 years old
- Usually rapid onset (e.g. < 1 month)
- **Headache** (found in **85%**)
- **Tender, palpable temporal artery**
- **Jaw claudication** (**65%**)
- **Visual disturbances** secondary to anterior ischemic optic neuropathy
- Systemic symptoms of **PMR**: **lethargy**, aching, morning **stiffness** in proximal limb muscles (**not weakness**), depression, low-grade fever, anorexia, night sweats, loss of weight.
- Transient ischaemic attacks (TIA).

In **elderly** people **GCA** is a **common presentation** of **acute monocular visual loss**.

**Investigations:**

- **ESR > 50 mm/hr.** (note that ESR < 30 in 10% of patients).
- CRP may also be elevated
- **Temporal artery biopsy (TAB)**: skip lesions may be present
- **CPK and EMG normal**

It is important to note that the **pathological findings** of giant cell arteritis (GCA) **persist for one to two weeks following initiation of corticosteroid**, and therefore treatment should not be delayed to obtain a biopsy.

لا تنتظر أخذ عينة ونتيجة الباثولوجى ... ابدأ كورتيزون فوراً ثم رتب لأخذ العينة

**Treatment:**

- Should be started immediately as soon as possible with **high-dose prednisolone (1mg/kg/day)** to reduce the chance of visual loss which is usually irreversible - there should be a dramatic and diagnostic response, if not the diagnosis should be reconsidered.
- Prednisolone therapy should not be delayed because involvement of the ophthalmic arteries can cause sudden unilateral irreversible visual loss.
- Bone protection and proton-pump inhibitors should be co-prescribed.
- Aspirin 75 mg OD is sometimes given as an adjunct but higher doses are not recommended.
- Urgent ophthalmology review. Patients with visual symptoms should be seen the same-day by an ophthalmologist. Visual damage is often irreversible.

As soon as the diagnosis is suspected, high dose corticosteroids should be given. Current BSR guidelines recommend:

- **Uncomplicated GCA** (no jaw or tongue claudication, or visual symptoms):  
**Prednisolone 40-60 mg daily.**
- **Complicated GCA:**
  - Evolving visual loss or history of amaurosis fugax: **IV methylprednisolone 500 mg-1 g daily for 3 days, followed by oral corticosteroids.**
  - Established visual loss: at least 60 mg prednisolone daily.

Symptoms usually **resolve quickly**, often **within 2 or 3 days**.

In around **75% of cases** need steroid therapy **between 1-3 years**.

Once they and laboratory abnormalities resolve, the dose of corticosteroid can be **reduced** and usually **stopped within 2 years**.

The patient should be **monitored for recurrence** throughout the taper: ESR every 4 weeks for 2-3 months, then every 8-12 weeks until 12-18 m after cessation of therapy.

**NB:** If clinical scenario is like GCA PLUS prominent peripheral blood eosinophilia, high IgE, Sinusitis, Positive P-ANCA >>> should lead you to a diagnosis of **Churg-Strauss**.

### Polymyalgia rheumatica (PMR)

Pathophysiology:

- Overlaps with temporal arteritis (GCA)
- The course of the disease is unpredictable, and 40% of patients also have giant cell arteritis.
- The cause is unknown, although studies showing a cyclical incidence have led to theories regarding an infectious trigger.
- Histology shows vasculitis with giant cells, characteristically 'skips' certain sections of affected artery whilst damaging others
- Muscle bed arteries affected most in polymyalgia rheumatica.
- Diagnosis of PMR can prove difficult, and other inflammatory conditions should be excluded.
- Patients are **usually over 60 years**, and PMR is very rarely seen in the under 50s.

**Features:**

- Typically patient ≥ 60 years old
- Usually rapid onset (e.g. < 1 month)
- **Pain & morning stiffness** in **proximal** limb muscles as **shoulder** and **pelvic** girdle muscles, classically symmetrical. (**Not weakness**).
- **Muscle weakness is NOT a feature of PMR**, but this can be difficult to assess in the presence of pain.
- **Muscle tenderness is NOT a specific feature of PMR**, and is not a classical finding. This is more suggestive of myositis or fibromyalgia.
- Also associated with a systemic inflammatory response and therefore constitutional symptoms as mild polyarthralgia, lethargy, depression, low-grade fever, anorexia, loss of weight, night sweats.

**Investigations:**

- CBC: Normochromic / normocytic anaemia.
- ESR > 40 mm/hr (although this may be normal).
- **CPK and EMG normal**
- Reduced CD8+ T cells
- PMR is **not** usually associated with an **elevated** RF, but it is important to note that this RF is present in 1-2% of the normal population.

**D.D:**

**Polymyositis** causes proximal muscle **weakness** in addition to pain, and **creatinine kinase** is typically raised.

**Polyarteritis nodosa (PAN)** is a small vessel vasculitis which does **not** commonly present with **isolated muscle** pain and stiffness. **Central** and **peripheral nervous** system signs are often present at diagnosis.

**Treatment:**

- **Prednisolone** (maximum dose not exceed **20 mg/OD**) >> dramatic response within 2-4 days (patients should report **70% improvement** in symptoms within 3 to 4 weeks, and inflammatory markers should have normalised by this point).
- Relapse is common after cessation or reduction of prednisolone ttt.
- The median ttt time is **2 years**, but some people require substantially longer.
- Calcium and vitamin D supplementation should be initiated for all patients with PMR who are starting corticosteroid therapy.
- Bisphosphonates should be added for long term steroid therapy.

- In general, NSAIDs have little use and are associated with significant morbidity.
- There is little evidence for the use of **steroid-sparing agents**.

**EX:** A 70-year-old man complains of **pain and stiffness in both his shoulders**. He has **lost one stone** in the last 8 weeks and complains of feeling **lethargic** with **loss of appetite**.

Labs: a **very high ESR (100 mm/hr)**, **normochromic normocytic anaemia** and a **positive RF**.

The most likely diagnosis >>> **PMR**.

**NB:** In **polymyalgia rheumatica (PMR)/ GCA** >>> proximal muscle **stiffness** but **not weakness** in an elderly patient.

But, **Weakness and muscle pain** are the predominant features of **polymyositis/IBM**.

### Takayasu's disease (TD)

It is a **continuous** or **patchy granulomatous** inflammatory process involving macrophages, lymphocytes, and multinucleated giant cells which causes progressive **occlusive** disease of the **aorta** and **its branches**.

It is **very rare** in the **western** world with an annual incidence of between 2 and 3 per million.

Approximately 80% of patients are **women**, and the mean age of onset is **30** years.

Clinical pictures:

- Presentation may be with **constitutional** symptoms such as fever, malaise, and weight loss;
- **Neurological** symptoms such as TIA; or vascular symptoms such as claudication.
- **Cardiac** features include angina, heart failure, and aortic regurgitation.
- **Renal**: mesangial proliferative GN.

TTT: Corticosteroids ± steroid sparing drugs (azathioprine or methotrexate).

With good care, 15-year survival rates approach 80%.

### **Cryoglobulinaemia**

**Immunoglobulins** which undergo **reversible precipitation at 4° C** and dissolve when warmed to 37°C. One third of cases are idiopathic.

This lead to **small vessels damage** in the limbs and deposition on the wall of small vessels result in **generalized vasculitis**, which presents with a reticulated skin pattern of **microthrombosis** and areas of **gangrene**.

**Pulmonary embolism, arterial and venous thrombosis** are common.

Recognized associations are chronic infections such as **HCV, SLE, RA** and **Sjogren's**

Three types:

- Type I (25%): monoclonal
- Type II (25%): mixed monoclonal and polyclonal: usually with RF
- Type III (50%): polyclonal: usually with RF

#### **Type I:**

- monoclonal - IgG or IgM
- associations: multiple myeloma, Waldenström macroglobulinaemia

#### **Type II:**

- mixed monoclonal and polyclonal: usually with RF
- associations: HCV, lymphoma, RA, Sjogren's

#### **Type III:**

- polyclonal: usually with RF
- associations: RA, Sjogren's

Symptoms (if present in high concentrations):

- Raynaud's only seen in type I
- Cutaneous: vascular purpura, ulcerations
- Arthralgia (Non-erosive polyarthralgia associates with hepatitis C).
- Polyneuropathy, Mononeuritis multiplex.
- Renal involvement (diffuse or Membranoproliferative glomerulonephritis)

**Palpable purpura, arthralgia and myalgia** (that is, **Meltzer's triad**) seen in cryoglobulinaemia (types II/III).

Tests:

- **High ESR**
- **Positive RF**
- **Low complement (esp. C4)**
- **Active urine sediments** (Blood++, protein ++)
- Serum cryoglobulins type II or III

In RA, RF is positive in 80% of patients, whereas in Sjogren's syndrome and cryoglobulinaemia, it is prevalent in up to 90% of cases.

Treatment:

- TTT of the underlying cause.
- Immunosuppression: Steroids and cyclophosphamide.
- Plasmapheresis.

**EX:** Female Pt 35 years old, arthralgia at hands, feet, wrist with Raynaud's phenomenon, tiredness, erythematous rash on both legs, high ESR 88, +ve RF, +ve ANA >>> Cryoglobulinaemia.

### Raynaud's

There is triad of colours: initial whitening of the fingers resulting from vasospasm, followed by blue discolouration and then reddening and pain.

Raynaud's phenomena may be:

- Primary (Raynaud's disease) or
- Secondary (Raynaud's phenomenon)

Raynaud's disease typically presents in young women (e.g. 30 years old) with symmetrical attacks.

Raynaud's **disease** (i.e **Primary**) presents in **young** women with **bilateral** symptoms

**Factors suggesting underlying connective tissue disease (i.e. secondary Raynaud's): ☹**

- Onset after 40 years
- Unilateral symptoms
- Rashes
- Presence of autoantibodies
- Features which may suggest RA or SLE, e.g. arthritis or recurrent miscarriages.
- Digital ulcers, calcinosis, gangrene or severe ischaemia of one or more digits.

- Very rarely: chilblains (pernio) are itchy, painful purple swellings which occur on the fingers and toes after exposure to the cold.

**Primary Raynaud's can be diagnosed if all the following are present:**

- No suspicion of underlying disease
- Symmetrical episodes affecting both hands, but not necessarily all fingers
- No tissue necrosis, ulceration, gangrene or severe ischaemia
- Normal nail-fold capillaries
- Normal ESR and negative anti-nuclear antibodies.

**NB:** Whilst it isn't a strict criteria given in the current guidance, it is recognised that episodes **typically terminate within 15 minutes** following **warming** in **primary** disease, but episodes tend to be **longer** in **secondary** Raynaud's and can be often in **excess of one hour**.

The most useful initial assessment to determine whether the Raynaud's is related to vasculitis or not >>> must include **nail fold capillary loop examination**, ideally by **capillaroscopy** or, if not available, by **ophthalmoscopy** using magnification >>> In CTD such as systemic sclerosis: dilated, distorted, missed nail fold capillary loops.

**Secondary causes:**

- Connective tissue diseases (CTD): **scleroderma** (most common), RA, SLE, PAN, Sjogren's syndrome.
- Type I cryoglobulinaemia, cold agglutinins.
- Leukaemia
- Polycythaemia.
- Thrombangitis obliterans (Buerger's disease)
- Use of vibrating tools
- Drugs: oral contraceptive pill, ergot (NB: Ergotamine rather than pizotifen is associated with Raynaud's phenomenon), BB, Vinblastine, Bleomycin.
- Cervical rib.

**Differential diagnosis of Raynaud's phenomenon includes:**

- Chilblains (perniosis): erythematous itchy swellings on fingers and toes in response to cold.
- Acrocyanosis: continuous blueness of the extremities aggravated by cold.
- Erythromelalgia: painful erythema caused by paroxysmal dilatation of blood vessels.
- Vascular embolism.
- Livedo reticularis.
- Mottled, cyanotic discolouration of skin.

**Management:**

- **Firstly supportive** ttt: patients should avoid exposure to the cold and stop drugs- induced Raynaud's phenomenon.
- First-line ttt: vasodilation by Dihydropyridine CCBs e.g. **Nifedipine MR**
- In severe forms, IV prostaglandin, endothelin-1 receptor antagonists and phosphodiesterase-5 inhibitors are used.
- IV prostacyclin infusions: effects may last several weeks/months.
- Future treatment options may include selective alpha-2c adrenergic receptor blockers, tyrosine and Rho-kinase inhibitors and calcitonin gene-related peptide.
- ACEIs and anti-platelets have been trialled in small case series, although no definitive benefit has yet been shown.

NB: Around 2% of women and 6% of men with Raynaud's phenomenon develop systemic sclerosis.
--

**Systemic sclerosis (SSc)**

It is a **chronic autoimmune** disease condition of **unknown** aetiology characterised by increased **fibroblast** activity and **fibrosis** in a number of different organ systems in the form of hardened, sclerotic skin and other connective tissues.

It is 4 times more common in **females**.

There are **three** patterns of disease:

**1) Limited cutaneous systemic sclerosis:**

- Raynaud's may be first sign
- Scleroderma affects face and distal limbs predominately
- Associated with **anti-centromere antibodies**
- CREST syndrome is an older term for the limited cutaneous form.
- **CREST syndrome** is a subtype of limited cutaneous systemic sclerosis: **C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasia
- Complications of CREST syndrome:
  - **Malabsorption** can develop in these patients secondary to bacterial overgrowth of the sclerosed small intestine (dysmotility secondary to infiltration of the intestinal wall with fibrous tissue).
  - Also, unfortunately **pulmonary hypertension** is one of the more common late complications seen in such patients.



- It is often difficult to distinguish between **interstitial lung disease** and pulmonary hypertension as the cause of breathlessness in systemic sclerosis.

**NB:** Lung involvement is a frequent complication of systemic sclerosis, and can be split into **2 main syndromes**: a pulmonary vascular disorder evolving over time into relatively isolated **pulmonary hypertension** and **interstitial lung disease**.

**EX:** Female pt. with SOB, lung fibrosis, GERD, Raynaud's, +ve ANA >> Systemic sclerosis.

## **2) Diffuse cutaneous systemic sclerosis**

- Scleroderma affects trunk and proximal limbs predominately
- Associated with **scl-70 antibodies**
- Hypertension, lung fibrosis and renal involvement seen
- Poor prognosis
- Whilst diffuse systemic sclerosis is associated with more severe and rapid internal organ involvement it is also seen in the limited form.

## **3) Morphea (Localized Scleroderma)** (without internal organ involvement)

- Tightening and fibrosis of skin
- May be manifest as plaques (**morphoea**) or linear.
- This is a **well-defined oval to round plaque**. (Like a painless lesion to his left subcostal region, dry, indurated and slightly coarse to palpation).
- The pathogenesis is poorly defined.
- An autoimmune component is suggested by enhanced T helper 2 (Th2) dependent interleukin 4 (IL-4) activity, which in turn up regulates transforming growth factor beta (TGF -beta). TGF-beta stimulates fibroblast production of collagen and other extracellular matrix proteins.
- Lab:
  - Elevated **ESR** and **CRP**.
  - **Hypergammaglobulinaemia** ( $\uparrow$ IgM, IgG),
  - Peripheral **eosinophilia** and
  - **Anti-Cu/Zn superoxide dismutase Ab** have been found in up to **90%**.

A major complication is the development of **scleroderma renal crisis (SRC)**:

This is characterised by the **abrupt** onset of **severe hypertension**, usually with **retinopathy**, together with **rapid deterioration of renal function** and **heart failure**.

Renal crisis is linked with a positive ANA speckled pattern, anti-RNA polymerase I and II antibodies and absence of anti-centromere antibodies.

The clinical presentation is **typically** with the symptoms of **malignant hypertension**: Headaches, Hypertensive retinopathy associated with visual disturbances, Seizures, Heart failure and pulmonary oedema.

Renal biopsy is not necessary in patients presenting with classical features of renal crisis.

The hypertension is almost always severe with a **diastolic BP over 100 mmHg** in **90%** of patients.

There is **hypertensive retinopathy** in about **85%** of patients with exudates and haemorrhages and if severe, **papilledema**.

There may also be **microangiopathic haemolytic anaemia** (↓ Hb with blood film shows schistocytes and helmet cells), **thrombocytopenia** and raised renin levels. **Renal function is impaired and usually rapidly deteriorates.**

Scleroderma renal crisis is **a medical emergency**. Aggressive treatment is required to prevent the occurrence of irreversible vascular injury.

**First line** treatment is a gradual reduction in blood pressure (10-15 mmHg per day) with an **oral ACEIs** until the diastolic pressure reaches 85-90 mmHg.

**ACEI** will improve hypertension and slow further renal impairment.

**ACEI** is the ttt of choice in **systemic sclerosis** with **renal disease** (↑ creat + HTN).

This approach leads to a **response in 90%** of patients by reversing the angiotensin-II mediated vasoconstriction.

An **abrupt fall** in BP should be **avoided** as it can further diminish renal perfusion and increase the risk of ATN. Therefore, **parenteral antihypertensive** agents (for example, IV nitroprusside or IV labetalol) should be **avoided**.

**CCBs**, usually **nifedipine**, may be added where there is inadequate reduction of BP with ACEI alone.

Additional oral hypotensive agents (for example, **labetalol**) can be used if required, and if pulmonary oedema is present a **nitrate infusion** may be indicated.

There is anecdotal evidence that IV prostacyclin helps the microvascular lesion without precipitating hypotension, and this is used in some UK centres.

**Antibodies:**

- 1) **ANA** positive in **90%**
- 2) **RF** positive in 30%
- 3) Anti-centromere antibodies associated with **limited** cutaneous S.S (CREST).
- 4) Anti-scl-70 antibodies associated with **diffuse** cutaneous S.S.(lungs)

Limited ( <b>central</b> ) <b>cutaneous</b> systemic sclerosis = anti- <b>centromere</b> antibodies
---

Although ANA is positive in 90% of patients with systemic sclerosis, anti-centromere antibodies are the most specific test for limited cutaneous systemic sclerosis

**Management:**

- Topical ttt for skin changes do not alter the disease course, but may improve pain and ulceration.
- NSAIDs.
- Steroids (limited benefit)
- CCB (Nifedipine)
- Bosentan (Dual Endothelin Receptor Antagonist)
- iloprost (Prostacyclin analogue)
- PDE-5 inhibitor.
- Methotrexate and cyclosporine.
- **Scleroderma renal crisis** >>>> **ACEI** (to control BP and delay progression to CRF)
- Active alveolitis >>>>> pulse cyclophosphamide + small dose steroids

**Dermatomyositis**

- Inflammatory disorder causing symmetrical, proximal muscle **weakness** and characteristic skin lesions.
- May be idiopathic or associated with connective tissue disorders or underlying malignancy (typically lung cancer, found in 20-25% - more if patient older, also oesophageal carcinoma).
- Polymyositis is a variant of the disease where skin manifestations are not prominent

Skin features:

- 1) Photosensitive.
- 2) **Shawl sign**: Macular rash over back and shoulder.
- 3) **Heliotrope rash** in the periorbital region and checks.
- 4) **Gotttron's papules** - roughened red papules over extensor surfaces of fingers at knuckles (pathognomonic).
- 5) **Telangiectasia** (Nail fold capillary dilatation).

Other features:

- **Proximal muscle weakness** +/- tenderness **with normal reflexes and sensation** and the **absence of fasciculations**.
- **Respiratory muscle weakness** with **decreased Vital capacity (VC)**
- Raynaud's
- Interstitial lung disease: e.g. Fibrosing alveolitis or organising pneumonia
- Dysphagia,
- Dysphonia
- The ocular muscles are very rarely involved unlike myasthenia gravis where this is a predominant feature.

**Investigations:**

- **↑ Creatine kinase** to 5-50 times the upper limit of normal.
- EMG
- **Skin and muscle biopsies are diagnostic for dermatomyositis.**
- ESR may be normal despite high disease activity.
- **ANA positive in 60%**
- **Anti-Mi-2 antibodies** are highly **specific** for **dermatomyositis**, but are only seen in around 25% of patients.
- **Anti-Jo-1 antibodies** are not commonly seen in dermatomyositis - they are more common in **polymyositis** where they are seen in a pattern of disease associated with interstitial lung disease involvement, Raynaud's and fever.
- **Screen for malignancy.** (Abd-pelvis US, Mammography, CT chest, PSA, PR)

**TTT:**

- **Prednisolone** is the **mainstay** of ttt, at an initial dose **1 mg/kg/day**. Most patients have a favourable response to corticosteroid therapy, and a 5-year survival rates approach 80%.
- When fail to show improvement, disease-modifying (methotrexate) or steroid-sparing agents (azathioprine) may be added.
- High protein diet and physiotherapy.

- Dermatomyositis antibodies >> **ANA most common, anti-Mi-2 Ab most specific.**
  - **Anti-Jo-1 antibodies** are more common in **polymyositis** than dermatomyositis especially with coexistent ILD, Raynaud's phenomenon.

Polymyositis is the commonest cause of inflammatory muscle disease in people under 50-years-old (inclusion body myositis is the commonest in those over 50-years-old).

**EX:** Female patient 50 years old, weakness, pain and tenderness of shoulder girdle and thigh muscle, discoloration around eyes, fingers telangiectasia, SOB, ↑ CPK 1000, ↑ESR, Anti-Jo-1 antibodies are positive >>> **Polymyositis** with **ILD**.

**EX:** Old male 60 years with intermittent dysphagia to liquids and solids, purple rash on his face, proximal muscle weakness can't get up out of the chair, +ve ANA >>> **Dermatomyositis** (NOT cancer oesophagus).

### Inclusion body myositis (IBM)

IBM is an inflammatory condition that affects **the over 50s**.

Proximal muscles and finger flexors are predominantly involved, but distal muscle groups may also be involved.

The **onset** of muscle **weakness** in IBM is generally **gradual (over months or years)**

IBM occurs more frequently in **men** than women.

There is **no** association of IBM with malignancy.

Creatine kinase (CK) may be normal.

EMG shows a similar pattern in polymyositis and IBM - small short duration motor unit arrhythmias can complicate polymyositis and dermatomyositis, but not IBM.

**Muscle Biopsy with electron microscopy:** in IBM shows intranuclear or cytoplasmic tubofilaments on electron microscopy.

Polymyositis and dermatomyositis show a much better response to steroids than IBM.

### Anti-synthetase syndrome.

Anti-synthetase syndrome associates with:

- **Raynaud's** phenomenon
- **Myositis**
- Fibrosing alveolitis, and
- Typical mechanic's hands (thickened, cracking, and peeling skin).
- **High CPK**
- **Positive Anti-Jo1 antibody**

### Mixed connective tissue disease

- Features of: SLE, systemic sclerosis and polymyositis
- **Anti-RNP positive**
- Ex pt. has arthralgia+myositis+Raynaud's: (Swollen hands with arthralgia, lethargy, muscle pains and Raynaud's phenomenon, +ve ANA, ↑CPK)

Anti-ribonuclear protein (anti-RNP) = mixed connective tissue disease

### Osteoarthritis: management

Osteoarthritis >>>>> **first-line**: paracetamol + topical NSAIDs (if knee/hand).

The **trapeziometacarpal joint (first carpometacarpal joint) (base of thumb)** is the most **common** site of **hand** osteoarthritis especially in **postmenopausal** women.

Osteoarthritis is one of the most common joint diseases, and its incidence is increasing with the **age** and **weight** of the population.

It presents with **pain**, commonly affecting the **knees**, **hips** and **small joints of the hand especially base of the thumb**.

There may be **bony swellings at distal and proximal IPJs**, termed Heberden's and Bouchard's nodes respectively.

Pathogenesis involves the **localised loss of cartilage**, with remodelling of adjacent bone. The associated **pain is exacerbated by exercise and relieved by rest**, although in advanced disease rest and night pain can develop. There may also be joint stiffness, typically in the morning or after rest.

NICE published guidelines on the management of osteoarthritis (OA) in 2008:

- 1) All patients should be offered help with weight loss, given advice about local muscle strengthening exercises and general aerobic fitness
- 2) Paracetamol is the **first**-line analgesics, then
- 3) Topical NSAIDs are indicated **only** for OA of the **knee** or **hand**, then
- 4) **Second**-line treatment is oral NSAIDs/COX-2 inhibitors, opioids, capsaicin cream and intra-articular corticosteroids. A PPI should be co-prescribed with NSAIDs and COX-2 inhibitors. These drugs should be avoided if the patient takes aspirin.
- 5) Non-pharmacological options: supports and braces, topical capsaicin, Application of heat or cold packs, TENS (Transcutaneous electrical nerve stimulation) and shock absorbing in soles or shoes.

- 6) If conservative methods fail then refer for consideration of joint replacement

**NB:** Treatments which are not NICE recommended include rubefacients, intra-articular hyaluronic, electro-acupuncture and chondroitin or glucosamine products.

What is the role of glucosamine?

- Normal constituent of glycosaminoglycans in cartilage and synovial fluid.
- A systematic review of several double blind RCTs of glucosamine in knee osteoarthritis reported significant short-term symptomatic benefits including significantly reduced joint space narrowing and improved pain scores.
- More recent studies have however been mixed.
- The 2008 NICE guidelines suggest it is **not** recommended
- A 2008 Drug and Therapeutics Bulletin review advised that whilst glucosamine provides modest pain relief in knee osteoarthritis it should **not** be prescribed on the NHS due to limited evidence of cost-effectiveness.

### **Paget's disease of the bone**

Paget's disease >>>> **old man, bone pain, raised ALP** (with **normal** Ca and PO4)

**EX:** Old man with **chronic back** and right **hip** pain for **several years** associated with **markedly elevated ALP** in the presence of **normal liver enzymes**, **normal calcium** and **normal ESR**, **difficulty hearing ± CHF** >>> Paget's disease.

- Paget's disease is a disease of increased but uncontrolled bone turnover.
- It is a **localised disorder of bone remodelling**.
- It is thought to be primarily a disorder of increased numbers of giant **osteoclasts**, with **excessive** osteoclastic resorption followed by increased osteoblastic activity in new bone formation and altered bone architecture.
- The structure of the new bone is disorganised and **mechanically weaker**, and therefore liable to **pathological fracture** and **deformity**.
- It can affect any bone, but is commonest in the **axial** skeleton, **long** bones and **skull**. The hands and feet are rarely affected.
- Both genetic and environmental factors are implicated, and it has been suggested paramyxovirus is involved.
- The **UK** has the **highest prevalence of Paget's disease** in the **world**.
- Paget's disease is common (UK prevalence 5%) but symptomatic in only 1 in 20 patients (5%).

Predisposing factors:

- Increasing age > 55 years
- Male sex



- Northern latitude
- Family history

Clinical features - only 5% of patients are symptomatic:

- Bone pain (e.g. pelvis, lumbar spine, femur)
- Classical, untreated features: bowing of tibia, bossing of skull
- **Raised alkaline phosphatase (ALP) - calcium\* and phosphate are typically normal.**
- Skull x-ray: thickened vault, osteoporosis circumscripta
- Femur x-ray: Radiolucency of subarticular region suggestive of **osteolysis and new bone formation**. Some areas of patchy **sclerosis**

NB: Calcium usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation.

To confirm the diagnosis of Paget's disease >>> **Skeletal survey**.

**Indications for treatment include** bone pain, skull or long bone deformity, fracture, nerve compression, periarticular Paget's:

- **Bisphosphonate** (oral risedronate or **IV zoledronate**): is the drug of choice.
- Calcitonin is less commonly used now due to anaphylaxis.
- **Serial monitoring of alkaline phosphatase** can help to **monitor** treatment.

**Serum ALP every 6 months** as a non-invasive method, appears to be the best way to **monitor** Paget's disease **activity**.

In Paget's disease, if the patient is **asymptomatic**, **No** need for treatment and he should just be **monitored**.

Complications:

- 1) **Deafness or tinnitus** (VIII cranial nerve entrapment): in up to **50%** of cases.
- 2) **Osteogenic sarcoma** (**1%** if affected for > 10 years) it carries a poor prognosis.
- 3) **Fractures**
- 4) **Skull thickening** and **spinal cord compression**
- 5) **High-output cardiac failure**

### **Osteopetrosis**

- Also known as marble bone disease
- Rare disorder of **defective osteoclast** function resulting in failure of normal bone resorption
- Results in dense, thick bones that are prone to fracture
- Bone pains and neuropathies are common.
- Calcium, phosphate and ALP are normal
- Stem cell transplant and interferon-gamma have been used for treatment



### Osteoporosis: causes

Risk factors:

- Family history
- Female sex
- Increasing age
- Premature menopause
- Smoking
- Low body weight with low BMI which lead to 2ry ovarian failure (NOT OBESITY)
- Deficient diet
- Sedentary lifestyle
- Caucasians and Asians

Diseases which predispose:

- Endocrine: glucocorticoid excess (e.g. Cushing's, steroid therapy), hyperthyroidism, hyperparathyroidism, hypogonadism (e.g. Turner's, testosterone deficiency), growth hormone deficiency, diabetes mellitus.
- Multiple myeloma, lymphoma.
- Gastrointestinal problems: inflammatory bowel disease, malabsorption (e.g. Coeliacs), gastrectomy, liver disease.
- Rheumatoid arthritis
- Long term heparin therapy\*
- Chronic renal failure
- Osteogenesis imperfecta, homocystinuria

\*Research is ongoing as to whether warfarin is a risk factor

**NB:** Long-term phenytoin therapy may cause enhanced vitamin D metabolism leading to osteomalacia, rather than osteoporosis.

### Osteoporosis: DEXA scan

Basics:

- T score: based on bone mass of young reference population
- T score of -1.0 means bone mass of one SD below that of young reference population
- Z score is refer to the bone mineral density compared with that of a 'normal' age matched subject adjusted for age, gender and ethnic factors

**T score:**

- $> -1.0$  = normal
- $-1.0$  to  $-2.5$  = osteopenia
- $< -2.5$  = **osteoporosis**

Osteoporosis in a man >>>>> check testosterone

**Osteoporosis** is diagnosed according to the World Health Organisation (**WHO**) and International Osteoporosis Foundation (**IOF**) criteria which state:

- **Normal**: hip BMD greater than the lower limit of normal which is taken as 1 SD below the young adult reference mean (**T score  $\geq -1$** ).
- **Osteopenia**: hip BMD between 1 and 2.5 DS below the young adult reference mean (**T score less than -1 but above -2.5**).
- **Osteoporosis**: hip BMD 2.5 SD or more below the young adult reference mean (**T score  $\leq -2.5$** ).
- **Severe osteoporosis**: hip BMD 2.5 SD or more below the young adult reference mean in the presence of one or more fragility fractures (**T-score  $\leq -2.5$  PLUS fracture**).

**Osteoporosis: glucocorticoid-induced**

Assessment for treatment - patients taking the equivalent of **prednisolone 7.5 mg or more each day for 3 months or longer**, and one of the following:

- 1) Over the age of 65 years
- 2) Have a history of a fragility fracture
- 3) Have a **T-score less than -1.5 SD**

The **T-score** of **less than -2.5** is indicative of osteoporosis. However **in patients on steroid therapy**, the T score of **less than -1.5 SD** is taken as a cut-off value to start osteoporosis therapy and an indication for a **bisphosphonate** and **Calcium** supplementation.

**Treatment:**

**Oral bisphosphonate** + this should be co-prescribed with **calcium + vitamin D**.

Pt. on **prednisolone  $\geq 7.5$  mg/day for  $\geq 3$  months with DEXA scans T-score less than -1.5 SD**

>>>> Oral bisphosphonate + Calcium supplementation + Vitamin D

## Bisphosphonates

Bisphosphonates are analogues of pyrophosphate, a molecule which decreases demineralisation in bone.

They **inhibit osteoclasts** by reducing recruitment and promoting apoptosis.

It is the **first** choice therapy for osteoporosis.

### Bisphosphonates >>> Inhibit osteoclasts

Clinical uses:

- 1) Prevention and treatment of osteoporosis
- 2) Hypercalcaemia
- 3) Paget's disease
- 4) Pain from bone metastases

Adverse effects:

- 1) **Oesophageal reactions:** esophagitis, oesophageal ulcers (especially alendronate).
- 2) **Osteonecrosis of the jaw:** pain in the jaw and ulceration within the oral cavity which has persisted for few weeks.
- 3) **Increased risk of atypical stress fractures** of the **proximal femoral shaft** in patients taking **alendronate**.

### The BNF suggests the following counselling for patients taking oral bisphosphonates

'Tablets should be swallowed whole with **plenty of water** while **sitting or standing**; to be given on an **empty stomach** at least **30 minutes before breakfast** (or another oral medication); patient should **stand or sit upright for at least 30 minutes after taking tablet**'

Guidelines for osteoporosis ttt recommend prescription of a **weekly generic bisphosphonates firstly**. For patients who fail to tolerate a weekly preparation, monthly oral or more intermittent IV preparations may be appropriate.

## Osteoporosis: secondary prevention

**RCP** guidance states that individuals should be given prophylaxis against osteoporosis if they:

- 1) Are **under 65** years
- 2) Require **steroids** for **longer than 3 months**, and
- 3) Have a **T score** of **less than -1.5**

The initial treatment of choice is a **bisphosphonate**. Only if bisphosphonates are not tolerated, would alternatives be considered.

**NICE** guidelines were updated in 2008 on the **secondary prevention of osteoporotic fractures in postmenopausal women**.

Key points include:

- Treatment is indicated following **osteoporotic fragility fractures** in postmenopausal women who are confirmed to have osteoporosis (a **T-score** of **- 2.5 SD or below**).
- In **women aged  $\geq 75$  years**, a **DEXA scan may not be required** 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'.

**EX:** A **77-year-old** woman is discharged following a fractured neck of femur. On review she is making good progress but consideration is given to secondary prevention of further fractures. What is the most suitable management? >>> **Start oral bisphosphonate without waiting for a DEXA scan in such scenarios.**

- **Alendronate** is first-line
- Around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered **Risedronate (Actonel ®)** or **Etidronate** (see treatment criteria below).
- Strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below).
- **Vitamin D and calcium** supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete.

**Treatment criteria for patients not taking alendronate:**

Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate.

These take into account a patient's age, their T-score and the number of risk factors they have from the following list:

- Parental history of hip fracture
- Alcohol intake of 4 or more units per day
- Rheumatoid arthritis

It is very unlikely that examiners would expect you to have memorised these risk tables so we've not included them in the revision notes but they may be found by following the NICE link. The most important thing to remember is:

- The T-score criteria for risedronate or etidronate are less than the others implying that these are the second line drugs
- If alendronate, risedronate or etidronate cannot be taken then strontium ranelate or raloxifene may be given based on quite strict T-scores (e.g. a 60-year-old woman would need a T-score < -3.5)
- The strictest criteria are for denosumab

### **Supplementary notes on treatment:**

#### **Bisphosphonates:**

- Alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis.
- All three have been shown to reduce the risk of both vertebral and non-vertebral fractures although Alendronate (Fosamax® 70 mg tab once weekly), Risedronate (Actonel® 35 mg tab once weekly) may be superior to etidronate in preventing hip fractures.
- Ibandronate Na (Boniva® 150 mg tab) is a once-monthly oral bisphosphonate.
- Despite daily, weekly, or monthly dosing, patients still suffer significant symptoms of indigestion (oesophagitis).

#### **Calcitonin:**

- Exogenous calcitonin **inhibits osteoclast activity**, and is associated with a 1-2% increase in BMD which is sustained for up to five years.
- Calcitonin is associated with a marked decrease in bone turnover, and consequently a decrease in urinary hydroxyproline excretion.
- In the absence of ADH, calcitonin increases sodium, potassium, calcium, and magnesium and chloride tubular resorption, thereby reducing their urinary excretion. It also decreases urinary hydroxyproline excretion.
- Rarely used due to **anaphylaxis**

#### **Vitamin D and calcium:**

- Poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures - may reduce rates in frail, housebound patients.

**Raloxifene - Selective Estrogen Receptor Modulator (SERM): ☺**

- Like tamoxifen is a SERM, with **oestrogen-like activity** at sites like **bone** (to increase mineralisation), but **anti-oestrogen-like effects** on **breast/endometrium** (preventing breast/endometrial hyperplasia).
- Has been shown to **prevent bone loss** and to **reduce the risk of vertebral fractures**, but has not yet been shown to reduce the risk of non-vertebral fractures.
- It increase bone density in the spine and proximal femur.
- May **worsen menopausal symptoms**
- **Increased risk of thromboembolic events**
- May **decrease risk of breast /endometrium cancer** ☺

**Strontium ranelate:**

- 'Dual action bone agent' - increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by inhibiting osteoclasts.
- Strong evidence base, may be second-line treatment in near future
- Increased risk of thromboembolic events

**Denosumab (XGEVA 120 mg vial ®AMGEN CO):**

- Human **monoclonal antibody** that inhibits the nuclear factor-kappa ligand (**RANK ligand inhibitor**) involved in osteoclast activation, which in turn **inhibits the maturation of osteoclasts**.
- RANK occurs on the surface of osteoclast precursors and osteoclasts. Inhibiting it leads to reduced osteoclast formation, function and survival. This leads to reduced bone reabsorption in both cortical and trabecular bone.
- It is as effective as intermittent bisphosphonate therapy and **inhibits pre-osteoclasts and osteoclasts**.
- Given as a **single SC injection every 6 months**.
- Initial trial data suggests that it is effective and well tolerated
- Especially used in severe esophagitis and can't tolerate daily alendronate.
- It has a **40% reduction in the risk of hip fracture over 3 years**.

**EX:** Old female 77 years old with **severe osteoporosis**, T score was measured at -4.2, she has suffered a previous **Colles' fracture**, and has a history of a **previous left leg DVT**. She was **unable to tolerate weekly alendronate** due to symptoms of **severe reflux esophagitis**.

The most appropriate alternative for her is >>> **Six monthly denosumab SC**.

**Teriparatide SC:**

- Recombinant form of PTH.
- It is synthetic PTH analogue.
- It is given SC injection.
- **Increased osteoblast activity**
- Very effective at increasing bone mineral density but role in the management of osteoporosis yet to be clearly defined.

**Hormone replacement therapy (HRT):**

- Has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures.
- Due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms.
- **Unopposed oestrogen therapy** is most appropriate if patient has had a **hysterectomy and oophorectomy**, and combined hormone replacement therapy (HRT) is unnecessary.
- Tibolone, Raloxifene and bisphosphonates are recommended as second line agents where HRT may be poorly tolerated or contra-indicated.

**Hip protectors:**

- Evidence to suggest significantly reduce hip fractures in nursing home patients
- Compliance is a problem

**Falls risk assessment:**

- No evidence to suggest reduced fracture rates
- However, do reduce rate of falls and should be considered in management of high risk patients

**EX:** A previously fit **47-year-old male** presents with lower back pain from a vertebral collapse due to **osteoporosis**.

Which is the most appropriate investigation for this man? **Testosterone**

**Osteoporosis** in a **young male** would be unusual >> **check testosterone**

### Tamoxifen

Tamoxifen is a Selective Estrogen Receptor Modulator (**SERM**) which acts as an oestrogen receptor **antagonist** and partial **agonist**.

It has both **oestrogen-like activity** at sites like **bone** (to increase mineralisation), but **anti-oestrogen-like effects** on **breast/endometrium** (preventing breast/endometrial hyperplasia).

It is used in the management of **oestrogen receptor positive breast cancer**.

It is usually taken **orally once a day** for **up to 5 years following removal of the tumour**, but for patients with metastatic disease it can be continued longer.

After surgical intervention, tamoxifen **reduces the risk of recurrence** of ductal carcinoma in situ and early stage invasive disease.

It confers a survival advantage of up to 4 years in postmenopausal women, and so it is given usually for 5 years after diagnosis.

It is even effective in women who **do not have a personal history** of breast cancer but who are **at increased risk** of the disease.

Due to its weak Estrogen like properties: slight decrease in total cholesterol in postmenopausal women ☺ and increase bone density ☺

Adverse effects (due to the weak Estrogen like properties) ☹

- 1) ↑ **Risk of Venous thromboembolism.**
- 2) ↑ **Risk of Endometrial cancer.**
- 3) **Medical menopause:** in the form of **menstrual disturbance:** vaginal bleeding, amenorrhoea and **hot flushes.**
- 4) **Indigestion and feeling sick**
- 5) **Weight gain**
- 6) **Vaginal dryness**
- 7) **Vaginal discharge**



8) Alopecia

9) Cataract

**Tamoxifen-induce medical menopause** with symptoms mimic to postmenopausal women like amenorrhoea and hot flushes which can be managed by adding **Megestrol** (Megace ®) , Medroxyprogesterone (Provera ®) and Norethisterone (Primolut N, Utovlan ®) ± antidepressants in low doses (SSRIs).

Hormone replacement therapy is not usually offered to women who have had breast cancer as it may increase the risk of breast cancer returning.

**Raloxifene** is a pure oestrogen receptor antagonist, and carries a lower risk of endometrial cancer.

### **Osteomalacia**

It results from inadequate mineralisation of the bone due to deficiency in Vit D.

Basics:

- **Normal bony tissue** but **decreased mineral content**
- **Rickets** if when growing
- **Osteomalacia** if after epiphysis fusion

Types:

- 1) **Vitamin D deficiency** e.g. malabsorption, lack of sunlight, diet
- 2) **Vitamin D resistant**; inherited
- 3) **Renal** failure
- 4) **Liver** disease, e.g. cirrhosis
- 5) **Drug** induced e.g. anticonvulsants
- 6) **Heavy metal poisoning** e.g. **mercury**: causes an acquired Fanconi syndrome with proximal (type 2) renal tubular acidosis.

Features:

- Rickets: knock-knee, bow leg, features of hypocalcaemia
- Osteomalacia: **bone pain, fractures, muscle tenderness, proximal myopathy**

Investigation:

- **Low calcium, low phosphate, low 25(OH) vitamin D**
- **Raised alkaline phosphatase**
- X-ray:
  - Children - cupped, ragged metaphysical surfaces;
  - Adults - translucent bands (**Looser's zones** or pseudo fractures):

**Osteomalacia X Ray >>> Looser's zones** it is **low density bands** extending from the cortex inwards in the shafts of long bones.

**Treatment:** calcium with vitamin D tablets

The best source of vitamin D is **Cod liver oil** which provides around 1,300 IU per 15 ml serving.

The **low calcium** and **low phosphate** combined with the **raised alkaline phosphatase** >>> point towards **osteomalacia**.

**Hypophosphatemia** is **only** present in **25%** of cases of osteomalacia, and therefore normal level should not preclude the diagnosis.

### **Osteogenesis imperfecta (brittle bone disease)**

Osteogenesis imperfecta (more commonly known as **brittle bone disease**) is a group of disorders of **collagen metabolism** resulting in bone fragility and fractures. The most common, and milder, form of osteogenesis imperfecta is type 1.

Overview:

- **Autosomal dominant.**
- Abnormality in **type 1 collagen** due to decreased synthesis of pro-alpha 1 or pro-alpha 2 collagen polypeptides.

Features:

- Presents in **childhood**
- Fractures following minor trauma
- Blue sclera
- Deafness secondary to otosclerosis
- Dental imperfections are common

### **Familial Mediterranean Fever (FMF)**

- Familial Mediterranean Fever (FMF, also known as recurrent polyserositis).
- It is an **autosomal recessive** disorder (**AR**) which typically presents by the second decade.
- It is more common in people of Mediterranean origin like Middle East, Turkish, Armenian, Syria, Lebanon, Egypt, Israeli (Jewish) and Arabic descent, but not exclusively.
- It relates to abnormal triggering of the inflammatory response and can lead to **AA type amyloid deposition** and therefore **renal failure**.
- However patients with this condition frequently take high doses of analgesics and anti-inflammatory drugs which put them at risk from analgesic nephropathy.

- Patient is recurrently admitted to hospital and undergo extensive investigations and often abdominal surgery, but no specific pathology is found.
- Abdominal symptoms **often mimic an acute surgical abdomen** and consequently many patients have undergone unnecessary laparotomy.
- Despite the severity of the symptoms during an attack, patients quickly recover and are well between episodes.

### **Features** - attacks typically **last 1-3 days**

- Pyrexia (on-off).
- Abdominal pain with even tenderness and guarding (due to **Peritonitis**) (appendectomy scar is seen dt multiple admission with Abd pain).
- **Constipation** accompanying the fever is common and **diarrhoea** may follow its resolution.
- **Pleurisy**
- **Pericarditis**
- **Arthritis** in 75% of cases.
- **High ESR and CRP.**
- **Erysipeloid rash on lower limbs**
- **FMF>>>> Renal amyloidosis>>>> Nephrotic syndrome (proteinuria) >>>> might need renal transplantation**

### **Diagnosis:**

- **MEFV gene analysis for FMF:** it confirm the suspected diagnosis.
- **Renal biopsy:** it is **diagnostic** for amyloid associate nephropathy and analgesic nephropathy.
- **Rectal biopsy** followed by examination with polarised light leading to “apple-green” birefringence: to confirm amyloidosis.
- **Serum Amyloid P component (SAP scan):** confirm the presence of amyloidosis.

The single most useful test to confirm the pathological basis of **amyloidosis** in **FMF** patient **when** develop **renal impairment** is >>> **Renal biopsy.**

### **Management:**

**Colchicine** is extremely effective in **treating** and **preventing** attacks of FMF (↓ attack frequency).

**NB:** Recurrent attacks of abdominal pain especially in young adults and may be misdiagnosed by surgeon >>> Think of **FMF** and **AIP** (Acute intermittent porphyria).

Whilst colchicine is of value in reducing amyloid deposition in FMF, there **is no evidence** that it has a **positive effect** in **amyloidosis** related to **other** underlying system inflammation like **rheumatoid arthritis**.

### **Avascular necrosis (AVN)**

- AVN may be defined as death of bone tissue secondary to loss of the blood supply. This leads to bone destruction and loss of joint function.
- It most commonly affects the epiphysis of long bones such as the humerus & femur.
- The main presentation is **pain** and **limitation of movements**.
- Both **night and rest pain** are present and **worsened with activity**.
- **Two forms** exist: **traumatic** and **atraumatic**.
- Traumatic form occurs in nearly all fractures of the anatomic neck as well as in fractures or dislocations of the humeral or femoral head.

Causes (risk factors for atraumatic form):

- **Long-term steroid use even low dose.**
- **Chemotherapy**
- Alcohol excess
- Haemoglobinopathies.
- Coagulopathies.
- Connective tissue disorders.

Features:

- Initially asymptomatic
- **Pain** in the affected joint

Investigation:

- **Plain x-ray findings may be normal initially**
- **MRI** is the investigation of choice. It is **more sensitive than** radionuclide bone scanning

### **Amyloidosis**

Secondary amyloid A (AA) amyloidosis is an important complication of **rheumatoid arthritis (RA)**.

It is caused by extracellular accumulation of AA fibrils, derived from the acute-phase-reactant **serum amyloid A protein**, within various tissues and organs.

It is a significant cause of increased morbidity and early death in RA. Studies have shown that deposits of AA fibrils are not uncommon in RA (~20%).

**Any patient with longstanding RA who develops proteinuria, or intractable diarrhoea, should be investigated for AA amyloidosis >>> Rectal biopsy.**

No blood test is diagnostic for amyloidosis.

Diagnosis therefore requires a **biopsy** and histological examination.

In order to start treatment as early as possible, a high-sensitivity site with a safe technique should be chosen. Subcutaneous fat, spleen, adrenal, liver, labia, salivary gland and gastrointestinal tract, **rectal** are frequent sites of AA amyloid deposition.

GI and rectal are recommended because their **sensitivities** are high and they can be performed as an **outpatient procedure**.

Non-invasive techniques, such as renal US, can be useful in assessing organ involvement, but cannot establish whether the findings are definitely related to amyloid.

The incidence correlates strongly with renal biopsy, but the procedure is associated with much lower risk.

Amyloidosis, as a **clinic-pathological descriptor** is used to denote the **in vivo**, **extracellular** deposition of material (**amyloid**) characterised by the following properties:

1. **Haematoxylin and eosin** staining - **amorphous eosinophilic** appearance
2. **Congo red** histological staining - **apple-green birefringence**
3. **Electron micrography** - **fibrillar appearance**
4. **X Ray diffraction** pattern - **beta pleated sheet structure**
5. **Solubility in water** and buffers of low ionic strength.

**Elbow pain**

The table below details some of the characteristic features of conditions causing elbow pain:

<b><u>Lateral epicondylitis (tennis elbow)</u></b>	<p>Features</p> <ul style="list-style-type: none"> <li>• It is most common in people aged 45-55 years and typically affects the <u>dominant arm</u>.</li> <li>• Typically follows unaccustomed activity such as <u>house painting</u> or <u>playing tennis</u> ('tennis elbow').</li> <li>• It is due to overuse/strain of the <b>extensor muscles of the forearm</b>.</li> <li>• Pain and tenderness localised to the lateral epicondyle</li> <li>• Pain worse on <u>resisted wrist extension with the elbow extended</u> or <u>supination of the forearm with the elbow extended</u></li> <li>• It is a self-limiting condition, episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks.</li> <li>• Supportive ttt: rest, ice, activity restriction, NSAIDs, Glyceryl trinitrate patches over the painful area and physiotherapy.</li> </ul>
<b>Medial epicondylitis (golfer's elbow)</b>	<p>Features</p> <ul style="list-style-type: none"> <li>• pain and tenderness localised to the medial epicondyle</li> <li>• pain is aggravated by wrist flexion and pronation</li> <li>• symptoms may be accompanied by numbness / tingling in the 4th and 5th finger due to ulnar nerve involvement</li> </ul>
<b><u>Radial tunnel syndrome</u></b>	<p>Most commonly due to compression of the posterior interosseous branch of the radial nerve. It is thought to be a result of overuse.</p> <p>Features:</p> <ul style="list-style-type: none"> <li>• Symptoms are <u>similar to lateral epicondylitis</u> making it <u>difficult</u> to diagnose</li> <li>• However, the pain tends to be <u>around 4-5 cm distal to the lateral epicondyle</u></li> <li>• Symptoms may be <u>worsened</u> by <u>extending the elbow</u> and <u>pronating the forearm</u></li> </ul>
<b>Cubital tunnel syndrome</b>	<p>Due to the compression of the ulnar nerve.</p> <p>Features</p> <ul style="list-style-type: none"> <li>• Initially intermittent tingling in the 4th and 5th finger</li> <li>• May be worse when the elbow is resting on a firm surface</li> </ul>

	or flexed for extended periods <ul style="list-style-type: none"> <li>• Later numbness in the 4th and 5th finger with associated weakness</li> </ul>
<b><u>Olecranon bursitis</u></b>	Swelling over the <u>posterior aspect of the elbow</u> . There may be associated <u>pain</u> , <u>warmth</u> and <u>erythema</u> . It typically affects <u>middle-aged male</u> patients.

### Adhesive capsulitis

Adhesive capsulitis (synonym, **frozen shoulder**) is a common cause of shoulder pain. It is most common in middle-aged patients. The aetiology of frozen shoulder is not fully understood.

Associations: **diabetes mellitus**: up to 20% of diabetics may have an episode of frozen shoulder

Features:

- On examination there is limited movement of the shoulder in all directions.
- external rotation is affected more than internal rotation or abduction
- both active and passive movement are affected
- patients typically have a painful freezing phase, an adhesive phase and a recovery phase
- bilateral in up to 20% of patients
- the episode typically lasts between 6 months and 2 years

Management:

- no single intervention has been shown to improve outcome in the long-term
- treatment options include NSAIDs, physiotherapy, oral corticosteroids and intra-articular corticosteroids

NB: Diabetic amyotrophy affects the lower limbs

### Rotator cuff muscles

**SlitS** - small t for teres minor

- **S**upraspinatus
- **I**nfraspinatus
- **t**eres minor
- **S**ubscapularis

Muscle	Notes
Supraspinatus	aBDucts arm before deltoid <u>Most commonly injured</u>
Infraspinatus	Rotates arm laterally
teres minor	aDDucts & rotates arm laterally
Subscapularis	aDDuct & rotates arm medially

### Carpal tunnel syndrome (CTS)

It is caused by compression of median nerve in the carpal tunnel.

History:

- Pain/pins and needles in thumb, index, middle finger
- Unusually the symptoms may 'ascend' proximally
- Patient shakes his hand to obtain relief, classically at night

Examination:

- Weakness of thumb abduction (abductor pollicis brevis)
- Wasting of thenar eminence (NOT hypothenar)
- Tinel's sign: tapping over median nerve course at wrist causes paraesthesia
- Phalen's sign: flexion of wrist causes symptoms

Causes:

- Idiopathic
- Alcoholism
- DM
- Hypothyroidism
- Oestrogen level: OCPs and Pregnancy
- Obesity
- Cushing syndrome
- Rheumatoid arthritis
- Oedema e.g. heart failure
- Lunate fracture

Investigations:

- Electrophysiology (nerve conduction studies): motor + sensory: prolongation of the action potential.



- Measure pressure in the carpal tunnel: **> 30 mmHg** would be considered abnormal.

Treatment:

- **Medical** ttt with local corticosteroid injection and wrist splinting at night: is associated with complete relief in only 22% of patients at one year.
- **Surgical decompression** via **incision flexor retinaculum** is the ttt of choice.

Unfortunately, patients commonly resent late, when some established nerve damage is inevitable.

### De Quervain's tenosynovitis

De Quervain's tenosynovitis is a common condition in which the sheath containing the extensor pollicis brevis and abductor pollicis longus tendons is inflamed.

It typically affects females aged 30 - 50 years old.

Features:

- Pain on the radial side of the wrist
- Tenderness over the radial styloid process
- Painful abduction of the thumb against resistance
- Finkelstein's test: with the thumb is flexed across the palm of the hand, pain is reproduced by movement of the wrist into flexion and ulnar deviation

Management:

- Analgesia
- Steroid injection
- Immobilisation with a thumb splint (spica) may be effective
- Surgical treatment is sometimes required

### Dactylitis

- Dactylitis describes the inflammation of a digit (finger or toe).
- A 'sausage-shaped' digit is a classical description of dactylitis.
- Dactylitis is not a feature of rheumatoid arthritis.
- Ex. Pt. with inflamed 2nd metatarsophalangeal joint

Causes include:

- Spondyloarthritis: e.g. Psoriatic and reactive arthritis
- Sickle-cell disease
- Other rare causes include tuberculosis, sarcoidosis and syphilis

**Ankle injury: Ottawa rules**

The Ottawa Rules with for ankle x-rays have a sensitivity approaching 100%.

An ankle x-ray is required only if there is **any pain in the malleolar zone** and any one of the following findings:

- **Bony tenderness at the lateral malleolar zone** (from the tip of the lateral malleolus to include the lower 6 cm of posterior border of the fibular)
- **Bony tenderness at the medial malleolar zone** (from the tip of the medial malleolus to the lower 6 cm of the posterior border of the tibia)
- **Inability to walk four weight bearing steps immediately after the injury** and in the emergency department

There are also Ottawa rules available for both foot and knee injuries

**Lower back pain (LBP)**

Lower back pain (LBP) is one of the most common presentations seen in practice.

Whilst the majority of presentations will be of a non-specific muscular nature it is worth keeping in mind possible causes which may need specific treatment.

Red flags for lower back pain:

- Age < 20 years or > 50 years
- History of previous malignancy
- Night pain
- History of trauma
- Systemically unwell e.g. weight loss, fever

The table below indicates some specific causes of LBP:

<b>Facet joint</b>	<p>May be acute or chronic</p> <p>Pain worse in the morning and on standing</p> <p>On examination there may be pain over the facets. The pain is typically worse on extension of the back</p>
<b>Spinal stenosis</b>	<p>Usually <b>gradual</b> onset</p> <p>Unilateral or bilateral <b>leg pain</b> (with or without back pain), numbness, and weakness which is worse on walking. Resolves when sits down. Pain may be described as 'aching', 'crawling'.</p> <p><b>Relieved by sitting down, leaning forwards and crouching down.</b></p> <p><b>Clinical</b> examination is often <b>normal</b>.</p> <p>Requires <b>MRI</b> to confirm diagnosis.</p>
<b>Ankylosing spondylitis</b>	<p>Typically a young man who presents with lower back pain and stiffness</p> <p>Stiffness is usually worse in morning and improves with activity</p> <p>Peripheral arthritis (25%, more common if female)</p>
<b>Peripheral arterial disease</b>	<p>Pain on walking, relieved by rest</p> <p>Absent or weak foot pulses and other signs of limb ischaemia</p> <p>Past history may include smoking and other vascular diseases</p>

### Lower back pain: prolapsed disc

A prolapsed lumbar disc usually produces clear dermatomal leg pain associated with neurological deficits.

Features:

- **Leg pain usually worse than back**
- **Pain often worse when sitting**
- **Positive stretch test (femoral / sciatic nerve)**

The table below demonstrates the expected features according to the level of compression:

Site of compression	Features
<b>L3</b> nerve root compression	Sensory loss over anterior <b>thigh</b> Weak quadriceps Reduced knee reflex Positive femoral stretch test
<b>L4</b> nerve root compression	Sensory loss anterior aspect of <b>knee</b> Weak quadriceps Reduced knee reflex Positive femoral stretch test
<b>L5</b> nerve root compression	Sensory loss <b>dorsum of foot</b> Weakness in foot and big toe <b>dorsiflexion</b> Reflexes intact Positive sciatic nerve stretch test
<b>S1</b> nerve root compression	Sensory loss <b>posterolateral aspect of leg</b> and <b>lateral aspect of foot</b> Weakness in <b>plantar flexion</b> of foot Reduced ankle reflex Positive sciatic nerve stretch test

Management:

- Similar to that of other musculoskeletal lower back pain: analgesia, physiotherapy, exercises
- If symptoms persist then referral for consideration of **MRI** is appropriate.

**It is possible to identify the compressed nerve root by examining the power, sensation, reflexes in the upper lower limbs.**

Root	Dermatome distribution	Myotome distribution	Tendon reflex
C4	Upper outer shoulder	Shoulder abduction	Nil
C5	Outer arm, forearm	Shoulder abduction, elbow flexion	Bicep
C6	Index and thumb	Wrist extension	Supinator
C7	Middle finger centre of palm	Finger and elbow extension	Triceps
C8	Little finger, ulnar border of hand	Wrist/finger flexion	Finger jerk

### Charcot joint

In patients with **longstanding diabetes** and **peripheral neuropathy**, a **red hot swollen foot** should raise suspicion of Charcot neuroarthropathy.

Diagnosis is suggested by **severe joint destruction** with **minimal symptoms** and **surprisingly normal joint**.

First described in 1868 by Charcot in a patient with syphilis, but also seen in syringomyelia, diabetic neuropathy, spinal cord and peripheral nerve injury, leprosy, multiple sclerosis and meningocele.

Charcot neuropathy presents as a warm, swollen, erythematous foot and ankle, and infection is important to exclude.

The majority of patients are in their **50-60s**, and they often present in the latter stages of the disease.

It can occur in association with a variety of conditions, including leprosy, poliomyelitis, rheumatoid arthritis, although today **the most common cause is diabetes mellitus**.

The pathophysiology of Charcot neuroarthropathy is not completely understood, but is thought to **start with peripheral neuropathy**.

It is thought to occur due to **increased blood flow** as a result of **neuropathy**, this results in **increased osteoclast activity** and **bone turnover**, the foot is then susceptible to often **very minor trauma** and **destructive changes** take place.

The **lack of pain sensation** may mean that patients subject the foot joints (commonly the **mid-foot at tarsal metatarsal joints**) to **stress injuries** that lead to the **Charcot process**.

It is important to note however that about half of patients present with pain.

Four stages of Charcot neuropathy are recognised:

- 1) **Stage 0 (inflammation):** characterised by erythema and oedema, but no structural changes.
- 2) **Stage 1 (development):** bone resorption, fragmentation and joint dislocation. Swelling, warmth and erythema persist but there are also radiographic changes such as debris formation at the articular margins, osseous fragmentation and joint disruption.
- 3) **Stage 2 (coalescence):** bony consolidation, osteosclerosis and fusion are all seen on plain radiographs.
- 4) **Stage 3 (reconstruction):** osteogenesis, decreased osteosclerosis, and progressive fusion. Healing and new bone formation occur, and the deformity becomes permanent.

**Radiographs** are an important part of investigating a patient with possible Charcot arthropathy. All radiographs should be taken **in the weight-bearing position**.

**MRI** can demonstrate changes in the earlier stages of the condition, and is therefore important in allowing treatment to be instigated earlier.

**Indium-labelled WBCs scan:** although it is not widely available, it is **the best** way to differentiate between infective causes of foot and Charcot's arthropathy.

In stages 0 and 1 the treatment is **immediate immobilisation** and **avoidance of weight-bearing**. A **total-contact cast** is worn until the redness, swelling and heat subside (generally 8-12 weeks, changed every 1-2 weeks to minimise skin damage). After this the patient should use a removable brace for a total of 4 to 6 months.

D.D: Osteomyelitis.

### **Treatment:**

- First line ttt is **total contact plaster and rest for at least 3 months** (immobilisation in a plaster cast for 3-6 months): this allow bone remodelling/repair to occur.
- Bisphosphonates can be used, but evidence of clinical benefit is lacking.
- Surgery is reserved for severe deformities that are susceptible to ulceration, and where braces and orthotic devices are difficult to use.

### **Complex regional pain syndrome (CRPS)**

CRPS is a **chronic pain** condition that can affect **any area of the body**, but often affects an arm or a leg, and occurs **after an injury** or **rarely after a sudden illness** such as a heart attack or stroke.

It is the modern, umbrella term for a number of conditions such as **reflex sympathetic dystrophy and causalgia**.

It describes a number of neurological and related symptoms which typically occur following surgery or a minor injury.

CRPS is **3 times** more common in **women**.

The condition can sometimes appear without obvious injury to the affected limb.

CRPS has two forms:

- **CRPS I** occurs in the absence of a preceding nerve injury (**NO** nerve injury)
- **CRPS II** is caused by an **injury** to the nerve.

The key symptom is pain that:

- Is intense and burning
  - Is disproportionate to the original injury
  - Is worse over time
  - Spreads beyond the site of injury and
  - Is associated with hyperalgesia, hyperpathia or allodynia on examination.
- These features do not occur in DVT, osteomyelitis, or cellulitis.

Features:

- **Progressive, disproportionate symptoms** to the **original** injury/surgery.
- Allodynia.
- **Temperature** and **skin** colour changes
- **Oedema** and sweating
- Motor dysfunction
- The Budapest Diagnostic Criteria are commonly used in the UK

CRPS may have 3 stages (acute, dystrophic, and atrophic), with variable progression from one stage to another.

CRPS is a **clinical diagnosis**, and various imaging modalities show non-specific changes which support its diagnosis:

- Plain radiographs may show soft tissue swelling, peri-articular osteoporosis, and rarely erosions.
- MRI may also show bone marrow oedema apart from these changes.
- <sup>99m</sup>Tc bone scan shows hypervascularity in the acute phase, and hypovascularity in the atrophic phase.

In the atrophic phase, imaging may show contractures.

Management:

- **Early physiotherapy** is important.
- **Neuropathic analgesia** in-line with NICE guidelines.
- Specialist management (e.g. Pain team) is required.

EX: A 38-year-old woman comes for review. Six months ago she fractured her left wrist whilst skiing. The fracture was treated using a cast and repeat x-rays showed that the bone had healed well. Unfortunately for the past few weeks she has been plagued with ongoing 'shooting pains' in her left hand associated with swelling. On examination the left hand is extremely tender to even light touch. Her left hand is also slightly swollen compared to the right.

What is the most likely diagnosis? >>>> **CRPS**.

### **Baker cyst (popliteal cyst)**

It is the most common mass in the popliteal area.

It is the results of synovial fluid distending the gastrocnemio-semimembranosus bursa rather than being a true cyst.

Diagnosis by knee **US** or if in doubt **MRI** can be considered to confirm the origin of the cyst.

Complication: **rupture or dissection of fluid into the adjacent proximal gastrocnemius** muscle belly which results in **syndrome mimicking the symptoms of a DVT**.

To differentiate by using **Doppler US** >>> the vascular lumen is compressible (not compressible in DVT).

While **drainage** may be attempt, **recurrence** is common, and **spontaneous resolution** may itself occur over the course of 1-2 years.



**Medical conditions associated with popliteal cyst (in descending order):**

- Arthritides
- Osteoarthritis.
- Rheumatoid arthritis.
- Juvenile arthritis.
- Gout (NOT Pseudogout)
- Reiter's syndrome.
- Psoriasis.
- SLE.
- Internal derangement (meniscal tears, anterior cruciate ligament (ACL) tear, osteochondral fracture).
- Infection (septic arthritis, TB)
- Chronic dialysis.
- Haemophilia.
- Hypothyroidism.
- Pigmented villonodular synovitis.
- Sarcoidosis.

**EX:** Pt presented with a picture **like acute LL DVT, but with normal Duplex US** and he has a history of **previous behind knee swelling** before that >>> **Backer cyst.**

**Bone markers**

Bones are now recognised to be metabolically active, dynamic tissues, rather than merely acting as a skeletal structure and reservoir for mineral ions.

Interest in diseases such as osteoporosis has stimulated the search for markers of bone turnover.

Markers are useful for prediction of prognosis, prediction of fracture risk, assessing suitability for therapy and monitoring the success of therapy.

Markers of <b>bone formation</b> (are measured in serum)	Markers of <b>bone resorption</b> (are measurable in serum or urine)
<ul style="list-style-type: none"> <li>➤ <b>Bone-derived alkaline phosphatase.</b></li> <li>➤ Osteocalcin and</li> <li>➤ Procollagen type 1 propeptides.</li> </ul>	<ul style="list-style-type: none"> <li>➤ Teloptides (NTx and CTx)</li> <li>➤ Pyridinium cross-linking molecules</li> <li>➤ Tartrate-resistant acid phosphatase (TRAP) and</li> <li>➤ Hydroxyproline.</li> </ul>

Alkaline phosphatase is useful but not specific to bone.

Osteocalcin is the main non-collagenous protein in bone. During bone formation, osteoblasts make osteocalcin and release some of it into the circulation. Resorption may cause a smaller increase in serum osteocalcin.

Collagen is made from procollagen, with cleavage of N- and C-terminal peptides. These peptides can be measured but are not as sensitive or specific as bone alkaline phosphatase.

### **Miscellaneous**

**Iritis** is associated with conditions such as **Reiter's**, **Behcet's**, **psoriatic** arthropathy (about 20%) and **inflammatory bowel disease**.

The most likely organism to have been aspirated from the infected hip joint replacement prosthesis >>> **Propionibacterium acnes (PA)**: **Gram positive bacilli**, it is poorly virulent, symptoms of PA infection may occur many years after original arthropathy, it is sensitive to **penicillins**, **clindamycin** and **carbapenems**.

### **Causes of recurrent arthritis:**

- **Crystal arthritis** (gout or Pseudogout): the most common cause of recurrent arthritis.
- Systemic auto inflammatory disorders (periodic fever syndromes).
- Whipple's disease.
- Arthritis associated with hyperlipidaemia.
- Intermittent hydrarthrosis.

**EX:** Pt with recurrent arthritis but now is free >>> **ask the patient to report to the clinic during the next attack >>? Crystal arthritis for aspiration** during the attack

# Pharmaceuticals & Therapeutics



**Pharmacokinetics: metabolism**

Drug metabolism usually involves two types of biochemical reactions - phase I and phase II reactions:

- Phase I reactions: oxidation, reduction, and hydrolysis. Mainly performed by the P450 enzymes but some drugs are metabolised by specific enzymes, for example **alcohol dehydrogenase** and **xanthine oxidase**. Products of phase I reactions are typically **more active** and **potentially toxic**.
- Phase II reactions: conjugation. Products are typically **inactive** and **excreted in urine or bile**. Glucuronyl, acetyl, methyl, sulphate and other groups are typically involved.

Drug metabolism:

- Phase I: **Oxidation, Reduction, Hydrolysis**
- Phase II: **Conjugation**

The majority of phase I and phase II reactions take place in the **liver**.

Usually products of both phase I and II reactions are **less lipid solubility**.

**First-pass metabolism:**

This is a phenomenon where the concentration of a drug is greatly reduced before it reaches the systemic circulation due to hepatic metabolism.

As a consequence much larger doses are needed orally than if given by other routes. This effect is seen in many drugs, including:

- 1) **Aspirin**
- 2) **Isosorbide dinitrate**
- 3) **GTN** Glyceryl trinitrate
- 4) **Lignocaine**
- 5) **Propranolol**
- 6) **Verapamil**
- 7) **Isoprenaline**
- 8) **Testosterone**
- 9) **Hydrocortisone**

Questions concerning zero-order kinetics and acetylator status are also common in the exam.

### **Zero-order saturation pharmacokinetics:**

Zero-order kinetics describes metabolism which is independent of the concentration of the reactant.

This is due to **metabolic pathways becoming saturated** resulting in a **constant amount** of drug being **eliminated** per **unit time**.

This explains why people may fail a breathalyser test in the morning if they have been drinking the night before.

Drugs exhibiting zero-order kinetics:

- 1) **Ethanol**
- 2) **Phenytoin**
- 3) Salicylates (e.g. high-dose aspirin)
- 4) Heparin
- 5) Warfarin
- 6) Theophylline

### **Acetylator status:**

**50%** of the UK population are deficient in hepatic N-acetyltransferase.

Drugs affected by acetylator status:

- 1) **Isoniazid (INH).**
- 2) **Hydralazine**
- 3) **Procaainamide**
- 4) Dapsone
- 5) Sulfasalazine

It was previously thought that 'fast acetylators' were more at risk of isoniazid than other patients. Recent research now suggests however that **slow acetylators** are actually more likely to suffer hepatotoxicity.

**Fast acetylation** leads to **higher** blood levels of the **toxic metabolite** acetyl isoniazid and thus to an increase risk of **toxic hepatitis** which is 250 times more common than in slow acetylators.

**Slow acetylators**, on the other hand, may be associated adverse effects secondary to **higher drug concentrations**, which can lead to **peripheral neuropathy**.

### P450 enzyme system

Induction usually requires prolonged exposure to the inducing drug, as opposed to P450 inhibitors, where effects are often seen rapidly.

Inducers	Inhibitors
<ul style="list-style-type: none"> <li>➤ <b>Rifampicin</b></li> <li>➤ Antiepileptics: <ul style="list-style-type: none"> <li>○ <b>Phenytoin</b>,</li> <li>○ <b>Carbamazepine</b></li> <li>○ Barbiturates: <ul style="list-style-type: none"> <li>Phenobarbitone</li> </ul> </li> </ul> </li> <li>➤ <b>Griseofulvin</b></li> <li>➤ Smoking</li> <li>➤ <b>St John's Wort</b></li> <li>➤ <b>Chronic</b> alcohol intake</li> <li>➤ Quinidine.</li> <li>➤ Tetracycline</li> <li>➤ Nevirapine (NNRTI)</li> </ul>	<ul style="list-style-type: none"> <li>➤ <b>Isoniazid (INH).</b></li> <li>➤ Antibiotics: <ul style="list-style-type: none"> <li>○ <b>Ciprofloxacin / Levo</b>,</li> <li>○ <b>Erythromycin / Clarith</b></li> <li>○ <b>Co-trimoxazole.</b></li> </ul> </li> <li>➤ Quinupristin &amp; Dalfopristin ABx.</li> <li>➤ Sodium <b>valproate (Depakin)</b></li> <li>➤ <b>SSRIs</b>: fluoxetine, sertraline</li> <li>➤ <b>SNRIs</b>: Venlafaxine</li> <li>➤ <b>Cimetidine, Omeprazole</b></li> <li>➤ <b>Amiodarone</b></li> <li>➤ <b>Diltiazem &amp; Verapamil</b></li> <li>➤ Allopurinol</li> <li>➤ <b>Ketoconazole, fluconazole</b></li> <li>➤ <b>Metronidazole</b></li> <li>➤ <b>Acute</b> alcohol intake</li> <li>➤ <b>Cranberry juice</b> عصير التوت البري</li> <li>➤ <b>Grapefruit juice</b> جريب فروت</li> <li>➤ <b>Methylprednisolone</b> (high dose)</li> <li>➤ <b>UDCA (ursofalk)</b></li> <li>➤ Ritonavir (PI)</li> </ul>

The most important drugs that are affected by the P450 enzyme system:

- 1) **Warfarin**
- 2) **Amiodarone**
- 3) **Digoxin**
- 4) **Statins**
- 5) **Combined oral contraceptive pill**
- 6) **Phenytoin**
- 7) **Cyclosporine**
- 8) **Aminophylline**

**Enzyme inducer** → **induce** CYP1A2 isoenzyme, so **reducing** the effectiveness of the above mentioned drugs.

**Enzyme inhibitor** → **inhibit** CYP1A2 isoenzyme, so **increased** the effectiveness of the above mentioned drugs (↑ its levels → Toxicity).

Smoking affects **CYP1A2**, so that why smokers require more aminophylline.

Carbamazepine is an inducer of the P450 system. This in turn increases the metabolism of carbamazepine itself - auto-induction.

**Grapefruit juice** is potent **inhibitor** of the cytochrome P450 enzyme CYP3A4

Concomitant use of **atorvastatin** and **large amounts of grapefruit juice** should be avoided as it contributed to ↑ **statin-associated myotoxicity**

Multiple studies have demonstrated this interaction between **grapefruit juice** and **felodipine**. Felodipine is normally metabolised in the GI tract and liver by CYP3A4. Grapefruit juice contains bergamottin which **INHIBITS** CYP3A4, thereby **increasing the bioavailability of felodipine** and the risk of toxicity with **increase postural hypotension** especially in old patient.

A raised INR is a result of **inhibited** liver enzymes.

**Co-enzyme Q10** is similar to **Vit. K** and reduces warfarin's anticoagulant effect

HIV TTT: **HAART - P450 interaction:**

- Nevirapine (a NNRTI): **induces** P450.
- Protease inhibitors (PI) like Ritonavir: **inhibits** P450.

### P450 drug interactions: more detail

Whilst you are expected to know in broad terms what are the main inhibitors and inducers of the P450 system it is unlikely that you will be asked detailed questions about the individual enzyme systems.

It is worthwhile noting that the **most important** and **common reason** for drug interactions is the **P450 CYP3A4 system**.

The table below shows the main enzyme systems that are affected by common drugs. There is clearly a lot of overlap within the various P450 enzymes.

P450 system	Substrates	Inducers	Inhibitors
<b>CYP3A4</b>	Macrolides. Antiretrovirals. CCBs.	Carbamazepine. Phenytoin. Phenobarbitone. Rifampicin. St John's Wort.	Macrolides. Protease inhibitors (including ritonavir). Imidazoles.
CYP2D6	TCA. Antipsychotics.		SSRIs Ritonavir
<b><u>CYP2C9</u></b>	<b><u>Warfarin.</u></b> Sulfonylureas.	Rifampicin	Imidazoles Amiodarone Sodium valproate
CYP1A2	Theophylline	Smoking Omeprazole	Ciprofloxacin
CYP2E1	Alcohol	Chronic alcohol Isoniazid	

A 69-year-old man is started on warfarin dt atrial fibrillation. During warfarin loading it is noted that his INR rises much more rapidly than expected. Genetic variation in which P450 enzyme systems is most likely to explain this>> **CYP2C9.** **Warfarin is a substrate of CYP2C9.**

### St John's Wort

- St John's Wort (*Hypericum perforatum*), is an herbal antidepressant available over the counter (**OTC**) in the United Kingdom.
- Shown to be as effective as tricyclic antidepressants (TCA) in the treatment of **mild-moderate depression**, anxiety and sleep disturbance.
- Mechanism: thought to be **similar to SSRIs** (although **noradrenaline uptake inhibition** has also been demonstrated).



- NICE advise 'may be of benefit in mild or moderate depression, but its use should not be prescribed or advised because of uncertainty about appropriate doses, variation in the nature of preparations, and potential serious interactions with other drugs.

Adverse effects:

- **Profile in trials similar to placebo.**
- Can cause **serotonin syndrome**.
- **Inducer of P450 system**, therefore decreased levels of drugs such as warfarin, cyclosporine. The effectiveness of the combined oral contraceptive pill may also be reduced.

### Drug-induced pancytopenia

- 1) Cytotoxics
- 2) Antibiotics: Trimethoprim, Chloramphenicol
- 3) Anti-rheumatoid: Gold and Penicillamine
- 4) **Carbimazole** (It causes both agranulocytosis and pancytopenia)
- 5) Anti-epileptics: Phenytoin and **Carbamazepine**
- 6) Sulphonylureas: tolbutamide

### Gingival hyperplasia

Drug causes of gingival hyperplasia:

- 1) **Phenytoin**.
- 2) **Cyclosporine**.
- 3) **Calcium channel blockers** (especially **Nifedipine**).

Other causes of gingival hyperplasia include:

- **AML** acute myeloid leukaemia (myelomonocytic and monocytic types).

Gingival hyperplasia >>>> Phenytoin, Cyclosporine, CCBs and AML
---

### Drugs causing photosensitivity

Rash on the <b>forearms</b> and <b>face</b> is typical of a photosensitivity rash
---

Causes of drug-induced photosensitivity:

- Tetracyclines, Sulphonamides, Ciprofloxacin
- **Sulphonylureas**
- NSAIDs e.g. piroxicam
- **Thiazides**
- **Amiodarone**
- **ACEIs & ARBs**
- Psoralens

### Drugs causing ocular problems (Visual disturbance)

Cataracts:

- Steroids

Corneal opacities:

- **Amiodarone**
- Indomethacin

Optic neuritis:

- **Amiodarone**
- Ethambutol
- Metronidazole

Retinopathy:

- Chloroquine, quinine >> blindness

Yellow- green tinge in vision:

- **Digoxin**

Blue tinge in vision:

- **Sildenafil**

**Sildenafil** can cause both **blue discolouration** and **non-arteritic anterior ischaemic neuropathy**.

**Sildenafil** is a **PDE-5 inhibitor**, but at **high** dose it inhibits the activity of **PDE-6**, which is essential for the functioning of retinal rods cells. Inhibition of the enzyme leads to patients reporting blue tinged vision, particularly in low light conditions.

### Drug causes of urticaria

The following drugs commonly cause urticaria:

- **Aspirin**
- NSAIDs
- Penicillins
- Opiates

Aspirin is a common cause of urticaria

### Haemodialysis in drug overdose

Can be cleared with haemodialysis mnemonic: <b>BLAST</b>	Cannot be cleared with haemodialysis
1) <b>B</b> arbiturate. 2) <b>L</b> ithium. 3) <b>A</b> lcohol (methanol, ethylene glycol). 4) <b>S</b> alicylates. 5) <b>T</b> heophylline ( <u>charcoal</u> <u>haemoperfusion</u> is preferable).	1) BDZ 2) TCA 3) Beta-blockers 4) Digoxin 5) Dextropropoxyphene (Co- proxamol)

### Theophylline

Theophylline, like caffeine, is one of the naturally occurring methylxanthines.

The main use of theophyllines in clinical medicine is as a bronchodilator in the management of asthma and COPD.

The exact mechanism of action has yet to be discovered. One theory suggests theophyllines may be a **non-specific inhibitor of phosphodiesterase** resulting in an **increase in cAMP**. Other proposed mechanisms include antagonism of adenosine and prostaglandin inhibition.

Theophylline poisoning:

Features:

- Acidosis, Hypokalaemia
- Vomiting
- Tachycardia, arrhythmias
- Seizures

Management:

- Activated charcoal
- Charcoal haemoperfusion is preferable to haemodialysis

Theophylline is non-specific phosphodiesterase inhibitor, while sildenafil is phosphodiesterase type V inhibitor.

### Drug-induced liver disease

Drug-induced liver disease is generally divided into hepatocellular, cholestatic or mixed. There is however considerable overlap, with some drugs causing a range of changes to the liver.

**The following drugs tend to cause a hepatocellular (Hepatitis) picture:**

- 1) Alcohol
- 2) Paracetamol
- 3) **Halothane**
- 4) Phenytoin
- 5) Sodium valproate

- 6) MAOIs
- 7) Anti-tuberculosis: Rifampicin, Isoniazid, Pyrazinamide
- 8) Nitrofurantoin
- 9) **Statins**
- 10) Methyldopa
- 11) Amiodarone

**The following drugs tend to cause Mixed Cholestasis (+/- Hepatitis):**

- 1) **Oral contraceptive pill**
- 2) Antibiotics: **Flucloxacillin, Co-amoxiclav, Erythromycin, Azithromycin, Ciprofloxacin, Ofloxacin.**
- 3) Anabolic steroids, testosterone
- 4) **Phenothiazines:** Chlorpromazine, Prochlorperazine
- 5) **Sulphonylureas**
- 6) **Fibrates**
- 7) Rare reported causes: Nifedipine, Captopril

Co-amoxiclav (Augmentin) is notorious for causing **drug-induced jaundice**, often with a **mixed hepatitis/cholestatic** picture. A 4 week **delay** in symptoms and signs is not unusual.

The patient must be warned that this could **reoccur** if he is given co-amoxiclav again.

Because of cholestatic jaundice, prescription of co-amoxiclav is not recommended for longer than 14 days.

**Liver cirrhosis:**

- 1) Methotrexate
- 2) Methyldopa
- 3) Amiodarone

**Acute intermittent porphyria (AIP): drugs**

It is an **autosomal dominant** condition caused by a defect in **porphobilinogen deaminase**, an enzyme involved in the biosynthesis of haem.

It characteristically presents with **abdominal** and **neuropsychiatric** symptoms in **20-40 year olds**.

AIP is more common in **females** (5:1).

Drugs which may precipitate attack:	Safe Drugs
<ol style="list-style-type: none"> <li>1) <b>Alcohol</b></li> <li>2) <b>Benzodiazepines</b></li> <li>3) <b>Barbiturates (Thiopentone)</b></li> <li>4) <b>Halothane</b></li> <li>5) <b>Oral contraceptive pill</b></li> <li>6) <b>Sulphonamides</b></li> </ol>	<ol style="list-style-type: none"> <li>1) Aspirin</li> <li>2) Paracetamol</li> <li>3) Codeine</li> <li>4) Morphine</li> <li>5) <b>Chlorpromazine</b></li> <li>6) Beta-blockers</li> <li>7) Penicillin</li> <li>8) Metformin</li> </ol>

A 43-year-old man presents with known acute intermittent porphyria is brought to the Emergency Department by the police due to an acute psychosis. What is the most suitable drug for sedation? >> **Chlorpromazine (NOT BDZs)**.

**Steroid doses**

Equivalence:

- 1mg Dexamethasone = 7mg Prednisolone
- 1mg Prednisolone = 4mg Hydrocortisone

**DPH >>> 1:7:28**

دبابة 1728

**Dexamethasone** is roughly 30 times **more potent** than hydrocortisone.

### Corticosteroids

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular).

They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

Minimal glucocorticoid activity, very high mineralocorticoid activity,	Glucocorticoid activity, high mineralocorticoid activity,	Predominant glucocorticoid activity, low mineralocorticoid activity	Very high glucocorticoid activity, minimal mineralocorticoid activity
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betamethasone

This is clinically relevant as there are some situations where it is important to combine high glucocorticoid (anti-inflammatory) activity with minimal mineralocorticoid (fluid-retention) effects. A good example is the use of **dexamethasone** for patients **with raised intracranial pressure** secondary to **brain tumours**.

### Side-effects:

The side-effects of corticosteroids are numerous and represent the single greatest limitation on their usage.

Side-effects are more common with systemic and prolonged therapy.

Glucocorticoid side-effects:

- Endocrine: impaired glucose regulation, increased appetite/weight gain, hirsutism, and hyperlipidaemia.
- Cushing's syndrome: moon face, buffalo hump, striae.

- Musculoskeletal: **proximal myopathy**, osteopenia and osteoporosis rather than osteomalacia, avascular necrosis of the femoral head. (Osteoporosis >>> which leads to Vertebral collapse).
- Immunosuppression: increased susceptibility to severe infection, reactivation of tuberculosis.
- Psychiatric: insomnia, mania, depression, psychosis.
- GIT: peptic ulceration, acute pancreatitis.
- Ophthalmic: glaucoma, cataracts.
- Suppression of growth in children.
- Intracranial hypertension.

Mineralocorticoid side-effects:

- Fluid retention
- Hypertension

### **Selected points on the use of corticosteroids:**

- **Patients on long-term steroids** should have their doses **doubled** during **intercurrent illness**.
- The BNF suggests **gradual withdrawal** of **systemic** corticosteroids if patients have: received **more than 40mg prednisolone daily** for **more than one week**, received more than 3 weeks treatment or recently received repeated courses.

Patients on long-term steroids should have their doses doubled during intercurrent illness.

**Proximal myopathy, easy bruising and thin skin** are clinical features that are **most suggestive of Cushing's syndrome**.

Otherwise, abdominal striae, buffalo hump, and acanthosis nigricans are all features of obesity.



**Corticosteroids** are recognised to inhibit osteoblast activity and increase osteoblast apoptosis. This is thought to be a more important component in bone loss with respect to **steroid induced osteoporosis** versus any effect on osteoclasts.

Patients taking **7.5 mg or more of prednisolone daily for 3 months or longer** should be offered **osteoprotection**.

The most appropriate therapy advocated by the National Osteoporosis Society for the **prevention of steroid-induced osteoporosis** would be bisphosphonate therapy such as Didronel or alendronate.

These are the **only class** of drug shown to offer osteoprotection with steroid therapy.

**EX:** 26-year-old male **body builder** + azoospermia + Lab: **low FSH** and **low LH** but with **normal testosterone**.

The most likely diagnosis is **steroid-induced hypogonadism**.

**Body builders** may be involved in the illicit use of **anabolic and androgenic steroids**. These results are consistent with ongoing use of androgens. The hypogonadism if persistent may be treated with human chorionic gonadotropin.

### **Allopurinol**

Allopurinol is used in the prevention of gout.

It works by inhibiting xanthine oxidase which is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid.

#### **Indications for allopurinol:**

- 1) Recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'.
- 2) Tophi.
- 3) Renal disease.
- 4) Uric acid renal stones.
- 5) Prophylaxis if on cytotoxics or diuretics.
- 6) Patients with Lesch-Nyhan syndrome often take allopurinol for life.

Patients receiving CHOP for non-Hodgkin's lymphoma are at particular risk of tumour lysis syndrome and associated gout secondary to hyperuricaemia. Allopurinol is therefore normally co-prescribed to reduce this risk.

### Initiating allopurinol prophylaxis:

- Allopurinol **should not be started until 2 weeks after an acute attack has settled.**
- **Initial** dose of **100 mg OD**, with the dose titrated every few weeks to aim for a serum uric acid of  $< 300 \mu\text{mol/l}$ .
- **NSAID** or **colchicine** cover should be used when starting allopurinol.

### Interactions:

#### Azathioprine (Imuran):

- Metabolised to active compound 6-mercaptopurine.
- Xanthine oxidase is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid.
- Allopurinol can therefore lead to high levels of 6-mercaptopurine.
- A much reduced dose (e.g. 25%) must therefore be used if the combination cannot be avoided.

#### Cyclophosphamide:

- Allopurinol reduces renal clearance, therefore may cause marrow toxicity.

### **Antiarrhythmics: Vaughan Williams classification**

It is still widely used although it should be noted that a number of common drugs are not included in the classification e.g. adenosine, atropine, digoxin and Mg.

AP = action potential

Class	Examples	Mechanism of action	Notes
Ia	Quinidine Procainamide Disopyramide  + Amiodarone	Block <b>sodium</b> channels  <b><u>Increases</u></b> AP duration	Quinidine toxicity causes <b>cinchonism</b> (headache, tinnitus, thrombocytopaenia)  Procainamide may cause drug-induced lupus
Ib	Lidocaine Phenytoin Mexiletine Tocainide	Block <b>sodium</b> channels  <b><u>Decreases</u></b> AP duration	
Ic	Flecainide Propafenone Encainide	Block <b>sodium</b> channels  <b><u>No</u></b> effect on AP duration	
II	Propranolol Atenolol Bisoprolol Metoprolol	<b>Beta-</b> adrenoceptors antagonists	
III	Amiodarone Sotalol Ibutilide Bretylium	Block <b>potassium</b> channels	
IV	Verapamil Diltiazem	<b>Calcium</b> channel blockers	
V	Adenosine Digoxin K <sup>+</sup> ions Mg <sup>++</sup> ions	<b>OTHERS</b>	

**Beta-blocker overdose**

Features:

- Bradycardia
- Hypotension
- Heart failure
- Syncope

Management:

- 1) If symptomatic bradycardia then **atropine** should be used in the **first** instance.
- 2) In resistant cases to atropine: **glucagon IV (50-150 Mcg/Kg)** followed by **IV infusion** may be used:
  - a. Glucagon can be effective but this should be tried after atropine.
  - b. Glucagon has a positive inotropic action on the heart by raising the myocardial cAMP levels, and
  - c. It decreases ↓ renal vascular resistance.
  - d. So Glucagon is useful in patients with beta-blocker Cardiotoxicity.
- 3) **Cardiac pacing** should be **reserved** for patients **unresponsive** to pharmacological therapy.
- 4) Haemodialysis is **not** effective in beta-blocker overdose.
- 5) If taken within **one hour** of presentation, **activated charcoal** should be tried.

Beta-blocker overdose management >> <b>Atropine IV + Glucagon IV</b>
--

Doses of glucagon used are much higher than those conventionally used for reversing hypoglycaemia in diabetes, it is a <b>bolus of 3-10 mg</b> being required, <b>then 2-5 mg/hr by infusion.</b>
---

**Calcium channel blockers (CCB)**

CCBs are primarily used in the management of cardiovascular disease.

Voltage-gated calcium channels are present in myocardial cells, cells of the conduction system and those of the vascular smooth muscle.

The various types of calcium channel blockers have varying effects on these three areas and it is therefore important to differentiate their uses and actions.

**Mode of action:** ↓ Ca entry to smooth and cardiac muscle which in turn results in a ↓ force of contraction and slower heart rate.

**Indications:**

- HTN
- Angina
- Arrhythmias (narrow complex tachycardia)
- Raynaud's

Examples	Indications & notes	Side-effects and cautions
<b>Verapamil</b>	Angina, hypertension, arrhythmias.  Highly negatively inotropic.  <b>Should not be given with beta-blockers as may cause heart block.</b>	Heart failure, constipation, hypotension, bradycardia, flushing.
<b>Diltiazem</b>	Angina, hypertension.  Less negatively inotropic than verapamil but caution should still be exercised when patients have heart failure or are taking beta-blockers.	Hypotension, bradycardia, heart failure, ankle swelling.
<b>Nifedipine, Amlodipine, Felodipine (dihydropyridines)</b>	Hypertension, angina, Raynaud's.  Affects the <b>peripheral vascular smooth muscle</b> more than the myocardium and therefore do not result in worsening of heart failure.	Flushing, headache, ankle swelling

**Dipyridamole**

Dipyridamole is an antiplatelet mainly used in combination with aspirin after an ischaemic stroke or transient ischaemic attack.

Mechanism of action:

- **Inhibits phosphodiesterase**, elevating platelet cAMP levels which in turn reduce intracellular calcium levels.
- Other actions include reducing cellular uptake of adenosine and **inhibition of thromboxane synthase**.

Dipyridamole inhibits phosphodiesterase
---

**Loop diuretics**

**Furosemide (Lasix ®)** and **Bumetanide (Burinex ®)** are loop diuretics that act by **inhibiting the Na-K-Cl cotransporter** in the **thick ascending limb of the loop of Henle**, reducing the absorption of NaCl.

The name of <b>Lasix</b> is derived from <b>lasts six</b> (hours) referring to its duration of action.
--

Indications:

- 1) **Heart failure**: both acute (usually IV) and chronic (usually orally).
- 2) **Resistant hypertension**, particularly in patients **with renal** impairment.

Adverse effects:

- Hypotension
- Hyponatraemia
- Hypokalaemia
- Hypocalcaemia
- Hypochloraemic alkalosis (Hyper PH)
- Hyperglycaemia (less common than with thiazides)
- Hyperuricaemia Gout
- Ototoxicity
- Renal impairment (from dehydration + direct toxic effect)

**Bendroflumethiazide**

Bendroflumethiazide (bendrofluazide) is a thiazide diuretic which works by **inhibiting sodium absorption** at the **beginning (proximal part) of the distal convoluted tubule (DCT)**.

**Potassium is lost** as a result of:

- 1) **More sodium reaching the collecting ducts** causes the Na-K exchanger to release more K into the urine.
- 2) **Another** cause is **activation of the renin-angiotensin-aldosterone system (RAAS)** secondary to hypovolaemia.

Bendroflumethiazide >>> mechanism of hypokalaemia:

- 1) Increased sodium reaching the collecting ducts.
- 2) Activation of the renin-angiotensin-aldosterone.

Bendroflumethiazide has a role in the treatment of mild heart failure although loop diuretics are better for reducing overload.

The main use of bendroflumethiazide currently is in the management of **hypertension** (as part of the effect is due to vasodilatation) but recent NICE guidelines now recommend other thiazide-like diuretics such as **indapamide** and **chlorthalidone**.

Common adverse effects:

- 1) Dehydration
- 2) Postural hypotension
- 3) Hyponatraemia
- 4) Hypokalaemia
- 5) **Hypercalcaemia**
- 6) **Hyperuricaemia**
- 7) **Hyperglycaemia** Impaired glucose tolerance
- 8) Impotence

Rare adverse effects:

- 1) Agranulocytosis
- 2) Thrombocytopaenia
- 3) Photosensitivity rash
- 4) Pancreatitis

### **Spironolactone**

Spironolactone is an aldosterone antagonist which acts in **the distal convoluted tubule (DCT)**.

Indications:

- 1) Ascites: patients with cirrhosis usually develop a secondary hyperaldosteronism. So that relatively large doses such as 100 or 200mg up to 400 mg daily are often used.
- 2) Heart failure (see RALES study below).
- 3) Nephrotic syndrome.
- 4) Conn's syndrome.

Adverse effects:

- Hyperkalaemia
- Gynaecomastia

RALES:

- NYHA III + IV, patients already taking ACE inhibitor.
- Low dose spironolactone reduces all-cause mortality.

NB: In the setting of AF, spironolactone may be used if the patient is thought to be in heart failure (which is fairly common with atrial fibrillation). In addition, spironolactone has been shown to **reduce the recurrence rate of atrial fibrillation following cardioversion** and so it is possible it would be started for this reason.

### **Sildenafil**

Sildenafil is a **phosphodiesterase type V (5) inhibitor** used in the treatment of impotence.

Side-effects:

- 1) Visual disturbances e.g. **blue discolouration, non-arteritic anterior ischaemic optic neuropathy**.
- 2) Nasal congestion.
- 3) Flushing.
- 4) Headache.
- 5) Gastrointestinal side-effects.



Contraindications:

- 1) Hypotension.
- 2) Patients taking **Nitrates** and related drugs such as **Nicorandil**.
- 3) Recent **stroke** or **myocardial infarction**.
- 4) Non-arteritic anterior ischaemic optic neuropathy.
- 5) **Other patients in which PPD5 inhibitors should be used with caution are those with risk of priapism, such as sickle cell or multiple myeloma.**

The BNF recommends **avoiding alpha-blockers (e.g. Doxazosin) for 4 hours after sildenafil**.

Visual changes secondary to drugs:

- **Blue** vision: Viagra ('the blue pill')
- Yellow-green vision: Digoxin

### Adrenoceptors

#### Alpha-1:

- **Vasoconstriction**
- **Relaxation of GI smooth muscle**
- Salivary secretion
- Hepatic GNG

#### Alpha-2:

- Mainly **presynaptic: inhibition** of transmitter release (inc NA, Ach from autonomic nerves)
- Inhibits insulin
- Platelet aggregation

#### Beta-1:

- Mainly located in the heart
- Increase heart rate + force

**Beta-2**

- **Vasodilation**
- **Bronchodilation**
- **Relaxation of GI smooth muscle**

**Beta-3:**

- **lipolysis**

**Pathways:**

- All are **G-protein coupled**
- **alpha-1**: activate **phospholipase C** → IP3 → DAG
- **alpha-2**: **inhibit** adenylate cyclase
- **beta-1**: stimulate adenylate cyclase
- **beta-2**: stimulate adenylate cyclase
- **beta-3**: stimulate adenylate cyclase

**Adrenoceptors antagonists**

**Alpha antagonists:**

- Alpha-1: **Doxazosin**
- Alpha-1a: **Tamsulosin** - acts mainly on urogenital tract (ttt of BPH)
- Alpha-2: **Yohimbine**
- Non-selective: **Phenoxybenzamine** (previously used in peripheral arterial disease)

**Beta antagonists:**

- Beta-1: **Atenolol**
- Non-selective: **Propranolol**

**Carvedilol** and **labetalol** are mixed alpha and beta antagonists.

The ESC guidelines in 2009 for **peri-operative management** of patients undergoing **high risk vascular surgery** (as a large abdominal aortic aneurysm) recommends **prophylactic beta-blockers** for high risk vascular surgery (including those patients with COPD).

**Bisoprolol** is probably the best clinical choice in this case.

**Atenolol** is cardio-selective and long acting - reducing risk of postoperative myocardial ischaemia and tachycardia.

**Carvedilol** is non-selective and so has greater risk of exacerbating COPD.

**Oxprenolol** is undesirable because of its intrinsic sympathomimetic properties.

**Metoprolol** through selective is shorter acting.

**Sotalol** may be appropriate for paroxysmal AF, but NOT permanent AF.

### **Adrenoceptor agonists**

#### **Alpha-1 agonists:**

- Phenylephrine

#### **Alpha-2 agonists:**

- Clonidine

#### **Beta-1 agonists:**

- Dobutamine

#### **Beta-2 agonists:**

- Salbutamol

#### **Beta-3 agonists:**

- Being developed, may have a role in preventing obesity (stimulation causes lipolysis).

**Drug-induced impaired glucose tolerance IGT**

Drugs which are known to cause impaired glucose tolerance include:

- 1) **Steroids**
- 2) **Thiazides, furosemide** (less common)
- 3) **Tacrolimus, Cyclosporine**
- 4) **Interferon-alpha**
- 5) **Nicotinic acid (Vit. B3).**
- 6) Atypical antipsychotics e.g. **Olanzapine**

Beta-blockers cause a slight impairment of glucose tolerance. They should also be used with caution in diabetics as they can interfere with the metabolic and autonomic responses to hypoglycaemia.

**Statins**

Statins inhibit the action of **HMG-CoA reductase**, the rate-limiting enzyme in **hepatic cholesterol synthesis**.

Most circulating cholesterol is manufactured **internally**, in amounts of about 1000 mg/day, via carbohydrate metabolism through the HMG-CoA reductase pathway.

Adverse effects:

- **Myopathy:** (occurs in up to **5%** of those treated with statins)
  - Includes myalgia, myositis, rhabdomyolysis and asymptomatic raised creatine kinase.
  - ↑ CPK levels more than ten times normal.
  - **Risks factors** for myopathy include advanced age, female sex, low BMI and presence of multisystem disease such as DM.
  - Myopathy is more common in lipophilic statins (simvastatin, atorvastatin) than relatively hydrophilic statins (rosuvastatin, pravastatin, fluvastatin).
  - Myalgia can gradually improve with time, dose reduction, or changing to an alternative statin. Pravastatin and rosuvastatin are metabolised via different pathways when compared to simvastatin and atorvastatin. Pravastatin may be suitable for primary prevention, but in this high-risk secondary prevention patient, a stronger agent is required. **Rosuvastatin can be effective at even low doses (5-10 mg).**

- It may be exacerbated by the co-prescription of other drugs such as **CCBs (diltiazem and verapamil)**, **macrolide** antibiotics, fibrates, and **amiodarone** and **grapefruit** juice.
- **Liver impairment:** the 2008 NICE guidelines recommend checking LFTs at **baseline, 3 months and 12 months**.

Treatment with Statins should be **discontinued** if serum transaminase concentrations **rise to and persist at 3 times** the upper limit of the reference range.

- There is some evidence that statins may **increase the risk of intracerebral haemorrhage** in patients who've previously had a **stroke**. This effect is not seen in primary prevention. For this reason the Royal College of Physicians recommend **avoiding statins in patients with a history of intracerebral haemorrhage**.

Cytochrome P450 **inhibitors** >>> ↑ **CPK** >>> **Myopathy**

**EX:** A 67-year-old female is prescribed simvastatin for hyperlipidaemia. Which one of the following juice is most likely to interact with her medication? >> **Grapefruit juice** is a potent **inhibitor** of the cytochrome P450 enzyme CYP3A4.

Statins should be **discontinued** in **women 3 months before conception** due to the risk of **congenital defects**.

**Ezetimibe monotherapy** produces reductions in TC and LDL-C of around **20%** and since tolerability issues are likely to occur with another statin.

### **Who should receive a statin?**

- 1) **All people with established cardiovascular disease (Stroke, TIA, IHD, and PVD).**
- 2) NICE recommend **anyone with a 10-year cardiovascular risk ≥ 20%.**
- 3) The management of blood lipids in type 2 diabetes mellitus (T2DM) has changed slightly:
  - **Previously, all patients with T2DM > 40-years-old** were prescribed statins.
  - **Now, Patients > 40-years-old** who have no obvious cardiovascular risk (e.g. Non-smoker, not obese, normotensive etc.) and have a cardiovascular risk < 20%/10 years **do not need** to be given a statin.

Statins should be taken **at night (Last thing in the evening)** as this is when the majority of cholesterol synthesis takes place. This is especially true for simvastatin which has a shorter half-life than other statins.

Current NICE guidelines do **not** recommend a **target** cholesterol in **primary** prevention. (**NO Target level of lipid profile in primary prevention**).

Current guidelines for lipid lowering (for secondary prevention):

	Total cholesterol	LDL cholesterol
Joint British Societies	< 4.0	< 2.0
National Service Framework for CHD	< 5.0	< 3.0
SIGN 2007	< 5.0	< 3.0

#### Hyperlipidaemia: mechanism of action and adverse effects

The following table compares the side-effects of drugs used in hyperlipidaemia:

Drugs	Mechanism of action	Adverse effects
Statins	<b>HMG CoA reductase inhibitors.</b>	Myositis, deranged LFTs
Ezetimibe	It localises at the brush border of the small intestine,  So it <b>decreases cholesterol absorption in the small intestine.</b>	Headache
Nicotinic acid	Decreases hepatic VLDL secretion.  <b>Inhibit lipolysis</b> of adipocytes.	Flushing, pruritis, IGT, myositis
Fibrates	<b>Agonist of PPAR-alpha</b> therefore <b>↑lipoprotein lipase expression</b> so:  ↓ <b>LDL</b> by 5-25%, ↑ <b>HDL</b> by 15-30% and ↓ <b>TG</b> (via ↓VLDL) by 20-60%.	Myositis, pruritus, cholestasis, <u>GB stones</u>

Drugs	Mechanism of action	Adverse effects
Cholestyramine	Decreases bile acid reabsorption in the small intestine ( <b>Bile acid sequestration</b> ), up regulating the amount of cholesterol that is converted to bile acid.	GI side-effects
<b>OMACOR</b> (omega-3-acid ethyl esters)	<p><b>Increases peroxisomal beta-oxidation of fatty acids in the liver.</b></p> <p>It reduces triglycerides by different, independent effects in the liver.</p> <p>It reduces production of TG in the liver, as EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis.</p> <p>EPA and DHA also inhibit esterification of other fatty acids.</p>	

**NB:** **Fibrates** and **nicotinic acid** have been associated with myositis, especially when combined with a **statin**. So take warns about the concomitant prescription of fibrates with statins in relation to muscle toxicity.

#### Nicotinic acid

It is used in the treatment of patients with hyperlipidaemia, although its use is limited by side-effects.

As well as **lowering cholesterol and triglyceride** concentrations it also **raises HDL levels**.

Nicotinic acid >>> ↓ TC, ↓ TG, ↑ **HDL**.

Adverse effects:

- 1) **Flushing**
- 2) **Myositis**
- 3) **Impaired glucose tolerance**

**Cyclosporine**

Cyclosporine is an immunosuppressant was introduced in 1983 which decreases clonal proliferation of T cells by **reducing IL-2 release**.

It acts by binding to cyclophilin forming a complex which **inhibits calcineurin**, a phosphatase that activates various transcription factors in T cells.

Action of cyclosporine:

- Binds to cyclophilin forming a complex which **inhibits calcineurin**, a phosphatase that activates various transcription factors in T cells.
- Decreases clonal proliferation of T cells by **reducing IL-2 release**.

Cyclosporine + Tacrolimus >>>: <b>inhibit calcineurin</b> thus <b>decreasing IL-2</b> .
---

**Adverse effects of cyclosporine** (note how **everything is increased** - fluid, BP, K<sup>+</sup>, hair, gums, glucose):

- 1) **Nephrotoxicity**: (the most frequent)
- 2) **Hepatotoxicity**
- 3) Fluid retention
- 4) **Hypertension**
- 5) **Hyperkalaemia**
- 6) **Hypertrichosis**
- 7) **Hyperglycaemia** (Impaired glucose tolerance)
- 8) **Hyperlipidaemia**
- 9) **Hyperuricaemia** (gout)
- 10) Pancreatitis.
- 11) Increased susceptibility to severe infection
- 12) Gingival **hyperplasia**
- 13) **Coarse tremor**
- 14) Anaemia & Thrombocytopenia

Cyclosporine SE: everything is increased - fluid, BP, K <sup>+</sup> , hair, gums, glucose
--

<b><u>NB</u></b> : In post renal transplant, the 2 most common causes of declining renal function are <b>graft rejection</b> and <b>cyclosporine toxicity</b> .
---



Interestingly for an immunosuppressant, cyclosporine is noted by the BNF to be 'virtually non-myelotoxic'.

Indications:

- 1) Following organ transplantation
- 2) Rheumatoid arthritis
- 3) Ulcerative colitis
- 4) Pure red cell aplasia
- 5) Psoriasis (has a direct effect on keratinocytes as well as modulating T cell function)
- 6) Severe eczema in cases where conventional therapy has failed.

### Tacrolimus (Prograf®)

Tacrolimus is a macrolide used as an immunosuppressant to prevent transplant rejection. It has a very similar action to cyclosporine.

The action of Tacrolimus differs in that it binds to a protein called **FKBP** rather than cyclophilin.

Tacrolimus is **more potent than cyclosporine** and hence the incidence of organ rejection is less. However, nephrotoxicity and impaired glucose tolerance is more common.

**Mycophenolate mofetil (MMF)** inhibits inosine monophosphate dehydrogenase.

**Methotrexate** is an antimetabolite which inhibits dihydrofolate reductase.

**Azathioprine** a purine analogue that inhibits purine synthesis.

### Lithium

Lithium is mood stabilising drug used most commonly prophylactically in **bipolar** disorder but also as an adjunct in refractory depression.

It has a **very narrow therapeutic range (0.5-1.0 mmol/L)** and a long plasma half-life being excreted primarily by the kidneys.

Mechanism of action - not fully understood, two theories:

- Interferes with inositol triphosphate formation
- Interferes with cAMP formation

Adverse effects:

- 1) **Goiter In 40 %**, may lead to **hypothyroidism in 20 %**
- 2) **Polyuria** (secondary to **nephrogenic diabetes insipidus**)
- 3) Anorexia/Nausea/Vomiting, **diarrhoea**
- 4) **Fine tremor**
- 5) **ECG**: T wave flattening/inversion
- 6) **Weight gain**
- 7) **Hypercalcaemia** (Raise ↑ serum Ca)
- 8) **Hypermagnesaemia** (Raise ↑ serum Mg)

Lithium: <b>fine tremor</b> in chronic treatment, <b>coarse tremor</b> in acute toxicity.
---

<b>Lithium &gt;&gt;&gt; Hypothyroidism &gt;&gt;&gt; Hyperprolactinaemia &gt;&gt;&gt; Infertility</b>
--

"The common clinical side effects of the lithium are <b>goitre</b> in up to <b>40%</b> and hypothyroidism in about <b>20%</b> . Lithium increases thyroid autoimmunity if present before therapy. Treatment with <b>levothyroxine</b> is effective and <b>lithium therapy should not be stopped.</b> "
--

Monitoring of patients on lithium therapy:

- Inadequate monitoring of patients taking lithium is common - NICE and the National Patient Safety Agency (NPSA) have issued guidance to try and address this. As a result it is often an exam hot topic.
- **Lithium blood level** should 'normally' **be checked every 3 months**. Levels should be **taken 12 hours post-dose**.
- **Thyroid** and **renal** function should be checked **every 6 months**.
- **GGT** is the most sensitive measure of the effects of lithium on the liver.
- Patients should be issued with an information booklet, alert card and record book.

**Lithium toxicity**

Lithium toxicity generally occurs following concentrations **> 1.5 mmol/L**.

**Toxicity may be precipitated by:**

- 1) Dehydration
- 2) Diuretics (especially **Thiazide**): it may result in paradoxical salt & water retention and possible Lithium intoxication.
- 3) Renal failure
- 4) **NSAIDs**
- 5) **ACEI & ARBs**.
- 6) **CCB (Verapamil & Diltiazem)**
- 7) **Metronidazole** is the only antibiotic listed in the BNF that may interact with lithium.

**BNF** advises that **neurotoxicity** may be ↑ when lithium is given with **diltiazem** or **verapamil** but there is no significant interaction with amlodipine.

Atenolol, in contrast, is a relatively safer option for the treatment of hypertension in association with long term lithium use.

Alpha-blockers are not listed as interacting with lithium but they would not be first-line treatment for hypertension.

**Features of toxicity:**

1. **Coarse tremor** (a fine tremor is seen in therapeutic levels)
2. Anorexia, nausea, vomiting, diarrhea
3. **Ataxia, Nystagmus, Dysarthria, hyperreflexia**
4. Acute confusion, Seizure, Coma
5. **Cardiovascular** adverse effects are more likely to occur in the presence of underlying cardiac disease: hypotension, bradycardia and heart block.

**Management:**

- 1) Mild-moderate toxicity (levels less than 2mmol/L) may respond to **volume resuscitation with normal saline**.
- 2) In **severe** toxicity (as in **high** lithium level and **reduced GCS**) >>> **Haemodialysis** may be needed.
- 3) **Sodium bicarbonate** is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion.

In acute or chronic toxicity, a **lithium level of greater than 4 mmol/L** or features of **central nervous system** toxicity or **cardiac instability** are indications for **haemodialysis**.

Activated charcoal does **not** bind lithium effectively and is therefore ineffective except where co-ingestion of other poisons is suspected.

10% of patients who survive from severe lithium toxicity will be left with a neurological deficit.

**EX:** Pt with bipolar disorder on lithium then develop polyuria and weight gain >>? **D.I** >>> **admission for water deprivation test and ADH administration.**

#### Therapeutic drug monitoring (DL-CP)

Digoxin	At least <b>6 hrs post-dose</b> (to ensure adequate distribution)
Lithium	<ul style="list-style-type: none"> <li>Range = 0.5 - 1.0 mmol/l</li> <li>Take <b>12 hrs post-dose</b></li> </ul>
Cyclosporine	<b>Trough levels immediately before dose</b> (قبل الجرعة مباشرة)
Phenytoin	<b>Trough levels immediately before dose</b> (قبل الجرعة مباشرة)

#### Monoamine oxidase inhibitors (MAOIs)

Overview:

- Serotonin and noradrenaline are metabolised by monoamine oxidase (MAO) in the presynaptic cell.

Non-selective monoamine oxidase inhibitors (MAOI):

- EX. Tranylcypromine, Phenelzine.
- Used in the treatment of atypical depression (e.g. hyperphagia) and other psychiatric disorder.
- Not used frequently due to side-effects.

Adverse effects of non-selective monoamine oxidase inhibitors:

- Hypertensive reactions with **tyramine containing foods** e.g.
  - **Cheese**
  - **Pickled herring**(الرنجة المخللة)
  - **Bovril**
  - **Oxo**
  - **Marmite**
  - **Broad beans** (الفول)
- Anticholinergic effects.

### **Benzodiazepines (BDZs)**

Benzodiazepines **enhance** the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (**GABA**) by increasing the **frequency** of **chloride channels**.

<b>BDZs enhance the effect of GABA, the main inhibitory neurotransmitter</b>
--

They therefore are used for a variety of purposes:

- 1) Sedation
- 2) Hypnotic
- 3) Anxiolytic
- 4) Anticonvulsant
- 5) Muscle relaxant

Patients commonly develop a **tolerance** and **dependence** to benzodiazepines and care should therefore be exercised on prescribing these drugs.

The Committee on Safety of Medicines advises that benzodiazepines are only prescribed for a short period of time (2-4 weeks).

The BNF gives advice on how to withdraw a benzodiazepine. The dose should be withdrawn in steps of about 1/8 (range 1/10 to 1/4) of the daily dose every fortnight. A suggested protocol for patients experiencing difficulty is given:

- 1) Switch patients to the equivalent dose of diazepam.
- 2) Reduce dose of diazepam every 2-3 weeks in steps of 2 or 2.5 mg.
- 3) Time needed for withdrawal can vary from **4 weeks** to **a year or more**.

If patients withdraw too quickly from benzodiazepines they may experience **benzodiazepine withdrawal syndrome**, a condition **very similar to alcohol withdrawal syndrome**. This may occur up to 3 weeks after stopping a long-acting drug. Features include:

- 1) Insomnia
- 2) Irritability
- 3) Anxiety
- 4) Tremor
- 5) **Loss of appetite**
- 6) **Tinnitus**
- 7) **Perspiration** عرق
- 8) **Perceptual disturbances** اضطراب ادراکی
- 9) Seizures

BDZs antidote is >>> **Flumazenil**

**NB: Flumazenil** should **not** be given in an **unknown overdose** as it can often precipitate **seizures** especially in a **mixed** overdose with **tricyclics** (TCA) and benzodiazepines.

### Alcohol withdrawal

Mechanism:

- Chronic alcohol consumption enhances GABA mediated inhibition in the CNS (similar to BDZ) and inhibits NMDA-type glutamate receptors.
- Alcohol withdrawal is thought to lead to the opposite ( $\downarrow$  inhibitory GABA and  $\uparrow$  NMDA glutamate transmission).

Features:

- **Symptoms** start at **6-12 hours alcohol-free period**.
- Peak incidence of **seizures** at **36 hours**.
- Peak incidence of **delirium tremens** is at **72 hours**.

Approximately 20% of patients admitted to hospital for illnesses unrelated to alcohol are drinking at potentially hazardous levels, and it's therefore important to ask all patients about their alcohol use.

An abrupt reduction in alcohol intake in a person who has been drinking excessively for a prolonged period of time, for example as occurs on admission to hospital, may result in the development of alcohol withdrawal.

Symptoms typically present about 10 hours after a significant fall in blood alcohol levels.

The peak is on day 2, and by day 5 the symptoms are significantly better.

Minor withdrawal symptoms appear **6-12 hours** after cessation of alcohol and include:

- Insomnia
- Fatigue
- Anxiety, Tremor, Restlessness
- **Palpitations**
- **Anorexia, Nausea, Vomiting**
- Headache
- **Sweating**
- **Flushing**
- Depression
- Craving

**Alcoholic hallucinosis** can appear **12-24 hours** after stopping alcohol and includes **visual, auditory** and **tactile** hallucinations.

**Withdrawal seizures** can appear **36 hours** after cessation and are generalised tonic-clonic seizures.

**Alcohol withdrawal delirium ('Delirium tremens') (DTs)** can appear **72 hours** after cessation.

Onset is typically **3 to 7 days after cessation** of **chronic** alcohol ingestion.

Delirium tremens, is the most severe form of alcohol withdrawal, which should be treated as a **medical emergency**.

Delirium tremens is a hyper adrenergic state, and is often associated with sweating, tachycardia, hyperthermia, hypertension, tachypnoea, tremor, mydriasis, visual hallucination, obtundation and confusion.

Patients at increased risk are those with a previous history of delirium tremens or alcohol withdrawal seizures, those with a co-existing infection or abnormal liver function, and older patients. It is a clinical diagnosis.

Delirium tremens should be treated with oral lorazepam as **first-line** treatment.

If the symptoms persist, or the medication is refused, **parenteral lorazepam**, **haloperidol** or **olanzapine** should be given. Intensive care may be required.

**Mortality without** treatment is approximately **35%**, which reduces to 5% with early recognition and treatment.

Management:

- 1) **Benzodiazepines** it is the **first** line of treatment for withdrawal, if no underlying structural lesion is detected and the patient does not have an epileptic disorder, **no long term antiepileptic drug therapy** is indicated.
- 2) **Carbamazepine** at a starting dose of **800 mg** per 24 hours also effective in treatment of alcohol withdrawal.
- 3) Phenytoin is said NOT to be as effective in the treatment of alcohol withdrawal seizures.
- 4) **Thiamine** is also indicated in chronic alcoholism to reduce the risk of Wernicke's encephalopathy, but is not as immediately important as diazepam.

**Haloperidol** is best **avoided** because of the risk of causing **hypotension**.

Haloperidol may be used in the sedation of patients who are distressed and anxious and present a danger to themselves or others however in delirium tremens **it may lower the seizure threshold** and has no effect on the underlying pathophysiology.

**EX:** A 45-year-old man is admitted due to hematemesis. He drinks 120 units of alcohol a week. When is the peak incidence of **seizures** following alcohol withdrawal? >>> **36 hrs**.

**EX:** Male pt. admitted with **acute pancreatitis** and was being treated conservatively with IV fluids and **NPO** and was making good recovery, an arrest call was made approximately **36 hours after** his admission when he was found unconscious and in generalised tonic-clonic seizure. He eventually stopped fitting after a total of **30 mg diazepam** IVI.





These reactions may also occur with alcohol based products, for example, **alcohol based perfumes**.

Disulfiram is **contraindicated** in **cirrhosis** and **heart** disease, and **psychosis** is a relative contraindication for its use.

**NB:** Methanol, like ethanol, is metabolised by alcohol dehydrogenase to form formaldehyde. Formaldehyde is then further metabolised by aldehyde dehydrogenase to formic acid.

Formate formation leads to a severe metabolic acidosis, and crystals forming within the eye can lead to so called '**snow field**' **cataract formation**.

Inhibition of metabolism of methanol by alcohol dehydrogenase with either ethanol or fomepizole is the treatment of choice.

Ethanol reduces the calcium-dependent secretion of anti-diuretic hormone (ADH) by blocking channels in the neurohypophyseal nerve terminal, so that can explain why **people who drink excessive amounts alcohol develop polyuria**.

**Ethanol inhibits ADH secretion >>> polyuria**

**Nausea** associated with hangovers is mainly due to **vagal stimulation** to the vomiting centre. Following a particular severe episode of alcohol excess people may experience tremors. These are due to increased glutamate production by neurones to compensate for the previous inhibition by ethanol.

### **Wernicke's encephalopathy**

Wernicke's encephalopathy is a result of **thiamine deficiency**.

Most cases occur in those with a history of **chronic alcohol ingestion** however **malnutrition** of any cause is a risk factor.

The classic **triad** of features is:

- 1) **Encephalopathy** (confusion, drowsy, disoriented, agitation)
- 2) **Ataxia** and
- 3) **Oculomotor dysfunction** (usually **nystagmus** but also potentially lateral rectus palsies or conjugate gaze palsies).

TTT: High dose **vitamin B (Thiamine) replacement IVI** (Pabrinex)

Administration of IV glucose prior to giving thiamine can significantly **worsen** Wernicke's encephalopathy.

The neurological changes are reversible if there is prompt administration of thiamine. Failure to do this results in permanent neurological disability (Korsakoff's syndrome).

**Fetal alcohol syndrome**

It is associated with **(3)**:

- 1) **Mental** retardation.
- 2) **Growth** retardation.
- 3) **Mid-facial** abnormalities.

The foetus relies on maternal hepatic detoxification of alcohol.

Alcohol appears to cross freely between mother and foetus, yet the fetal liver has only 10% of the capacity of the adult liver to detoxify alcohol.

**Zieve's syndrome**

A combination of tetrad **(4)**:

- 1) **Alcoholic hepatitis,**
- 2) **Jaundice,**
- 3) **Hyperlipidaemia,** and
- 4) **Haemolysis with anaemia.**

There is **no specific treatment** for Zieve's syndrome but **supportive therapy** is indicated which includes

- Correction of clotting abnormalities.
- Treatment of haemolysis.
- Treating alcohol withdrawal.
- Preventing further alcohol intake.
- Adequate nutrition.

**Ethylene glycol toxicity**

Ethylene glycol is a type of alcohol used as a **Coolant** or **Antifreeze** used in cars.

Features of toxicity are divided into 3 stages:

<b><u>Stage 1</u></b> : Symptoms <b>similar to alcohol intoxication: confusion, coma, slurred speech, dizziness.</b>
<b><u>Stage 2</u></b> : <b>Severe metabolic acidosis with high anion gap and high osmolar gap, hyperventilation, kussmaul breathing, hypocalcaemia. Also Tachycardia, Hypertension.</b>
<b><u>Stage 3</u></b> : <b>Acute renal failure (caused by oxalate crystalluria).</b>

Ethylene glycol intoxication presents with DCL, severe high anion gap metabolic acidosis, renal, respiratory, cardiac failure.

**Multi-organ failure** is thought to occur at least in part due to widespread deposition of **calcium oxalate crystals** around 12 hrs after the initial insult.

Because of the possible formation of calcium oxalate, **calcium** level should be assessed.

Unfortunately with delayed presentation, ingestion of **relatively small amount** of ethylene glycol as little as **30 ml** is **fatal**.

Symptoms are: nausea, vomiting, convulsions, coma and respiratory distress with **no alcohol odour on the breath**. This differentiates ethylene glycol poisoning from other alcohols such as ethanol or methanol.

An **osmolar gap** exists when measured plasma osmolality is greater than **calculated** osmolality by **> 10 mOsmol/kg**.

**Calculated osmolality =  $2(\text{Na} + \text{K}) + \text{urea} + \text{glucose}$ .**

Several unmeasured osmotically active substances in the plasma such as ethanol. Methanol, ethylene glycol, mannitol and glycine are responsible for increased osmolar gap.

Management has changed in recent times:

- 1) **Ethanol** has been used for many years:
  - a. Works as a **competitive inhibitor** with ethylene glycol **for the enzyme alcohol dehydrogenase**.
  - b. This limits the formation of toxic metabolites (e.g. glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning.
- 2) **Fomepizole (4-methyl pyrazole)**, a **competitive inhibitor of alcohol dehydrogenase**, is now used first-line in preference to ethanol.
- 3) **Haemodialysis** also has a role in refractory cases of metabolic acidosis and acute renal failure.

**Fomepizole** is now used as the **first** line of ttt rather than ethanol in ethylene glycol toxicity. **Haemodialysis** is indicated **only in** refractory cases of metabolic acidosis and acute renal failure.

N.B: Loss of vision is seen in methanol rather than ethylene glycol poisoning

**EX:** 40 year old mechanic was brought unconscious to ER, he was found at the **garage** he owns by his wife having an **epileptic** fit with vomiting, he is previously fit and well, **no smell of alcohol**, Lab: **metabolic acidosis**, **hypocalcaemia**, **high serum osmolality**, urine: **oxalate crystals** >>> **Ethylene glycol poisoning**.

### **Methanol poisoning**

Methanol is sometimes used as a substitute for Ethanol by alcoholics, as it similarly causes inebriation.

Usually seen with **middle-aged homeless man**

Methanol poisoning causes both the effects associated with alcohol (intoxication, nausea etc.) and also specific visual problems, including **blindness**. These effects are thought to be secondary to the **accumulation of formic acid**.

Formic acid later produces a **metabolic acidosis** and **retinal injury**.

The actual pathophysiology of methanol-associated visual loss is not fully understood but it is thought to be caused by a form of **optic neuropathy**.

Management:

- **Fomepizole IV** or **Ethanol IV**
- **Haemodialysis:** Indications for HDx in methanol poisoning include:
  - 1) Low GCS level which points to a severe overdose.
  - 2) A methanol level > 0.5g/L.
  - 3) Renal impairment.
  - 4) Any visual disturbance.

**Fomepizole** - used in ethylene glycol and methanol poisoning - **competitive inhibitor of alcohol dehydrogenase**

### **Ecstasy poisoning** النشوة

Ecstasy (**MDMA**, 3,4-Methylenedioxymethamphetamine) use became popular in the 1990's during the emergence of **dance music culture at night clubbing**.

Clinical features:

- 1) **Neurological:** DCL, agitation, anxiety, confusion, ataxia, Dilated pupils
- 2) **DIC** (↓ **PLT**) and **Rhabdomyolysis** (↑**CPK**) >> **renal failure**
- 3) **Cardiovascular:** **tachycardia**, **hypertension**

4) **Hyperthermia** and **Hyperventilation**

5) **Hyponatraemia**

Ecstasy is thought to stimulate the production of anti-diuretic hormone **ADH**. Users of ecstasy also commonly drink too much water in the (mistaken) belief that this will protect them from the adverse effects.

Management:

- Supportive: ABC, BDZ for control of seizure, Na Nitroprusside for HTN, urinary alkalinisation for ↓ progression of ARF.
- **Dantrolene IV** may be used for hyperthermia if simple measures fail.

### **Cocaine**

Cocaine is an alkaloid derived from the coca plant.

It is widely used as a recreational stimulant.

The price of cocaine has fallen sharply in the past decade resulting in cocaine toxicity becoming a much more frequent clinical problem.

This increase has made cocaine a favourite topic of question writers.

**Mechanism of action:** Cocaine blocks the uptake of dopamine, noradrenaline and serotonin.

The use of cocaine is associated with a **wide variety of adverse effects:**

**Cardiovascular effects:**

- **Hypertension**
- Both **tachycardia** and bradycardia may occur
- Myocardial infarction
- Aortic dissection
- QRS widening and QT prolongation

**Neurological effects:**

- Mydriasis
- Hypertonia
- Hyperreflexia
- **Seizures**

**Psychiatric effects:**

- Agitation
- Hallucinations
- **Psychosis**

**Others:**

- **Hyperthermia**
- **Rhabdomyolysis**
- **Metabolic acidosis**
- **Renal failure**

**Management of cocaine toxicity:**

- In general **benzodiazepines IV** are generally first-line for most cocaine related problems.
- Chest pain: **benzodiazepines + glyceryl trinitrate**. If myocardial infarction develops then primary PCI.
- Hypertension: **benzodiazepines + sodium nitroprusside**.
- The use of beta-blockers in cocaine-induced cardiovascular problems is a controversial issue. The American Heart Association issued a statement in 2008 warning against the use of beta-blockers (due to the risk of unopposed alpha-mediated coronary vasospasm) but many cardiologists since have questioned whether this is valid. If a reasonable alternative is given in an exam it is probably wise to choose it.

**Oculogyric crisis**

An oculogyric crisis is an **acute dystonic reaction** to certain drugs or medical conditions due to **dopaminergic blockade** at the basal ganglion.

The effects usually occur within 72 hours but have been reported to occur within 30 minutes of starting treatment.

It is a form of **extrapyramidal** disorder.

**EX:** Abnormal head movements and has gone 'cross-eyed'. The neck is extended and positioned to the right. The eyes are deviated upwards and are slightly converged.

Features:

- 1) **Restlessness, agitation**
- 2) Involuntary **upward deviation of the eyes**

Causes:

- 1) Phenothiazines
- 2) Haloperidol
- 3) Metoclopramide
- 4) Post encephalitic Parkinson's disease

Management: Although **self-limiting**, the reaction can be reversed by:

- **Procyclidine HCL**
- **Trihexyphenidyl HCL** (formerly known as Benzhexol)
- **Benzotropine IV (Cogentin ®)**
- **Diphenhydramine** is alternative option.

### Palliative Care Prescribing

The **breakthrough dose** of morphine is **one-sixth** the daily dose of morphine.

All patients who receive opioids should be prescribed a **laxative**.

Opioids should be used with caution in patients with CKD. **Alfentanil**, **fentanyl** and buprenorphine are preferred.

Metastatic bony pain may respond to **NSAIDs**, **bisphosphonates** or **radiotherapy**.

### Conversion between opioids:

From	To	
Oral Codeine	Oral Morphine	Divide by <b>10</b>
Oral Tramadol	Oral Morphine	Divide by <b>5</b>
Oral Morphine	Oral Oxy-codone	Divide by <b>2</b>



The BNF states that oral morphine sulphate tablet (MST) 80-90 mg over 24 hours is approximately equivalent to one “25 mcg/hr” patch, therefore product literature should be consulted.

From	To	
Oral Morphine	SC dia-morphine	Divide by <b>3</b>
Oral Oxy-codone	SC dia-morphine	Divide by <b>1.5</b>

Underlying causes of **confusion** need to be looked for and treated as appropriate, for example hypercalcaemia, infection, urinary retention and medication.

If specific treatments fail then the following may be tried:

- First choice: **Haloperidol**
- Other options: Chlorpromazine, Levomepromazine

Management of hiccups:

- **Chlorpromazine** is licensed for the treatment of **intractable hiccups**.
- Haloperidol, Gabapentin and Baclofen are also used.

Hiccups in palliative care >> chlorpromazine or haloperidol
---

<b>EX:</b> A 65-year-old female with metastatic breast cancer is reviewed in clinic. Her husband reports that she is increasingly confused and occasionally appears to talk to relatives that are not in the room. Following investigations for reversible causes, the most appropriate management >>> <b>Haloperidol</b> .
---

In <b>the terminal phase of the illness</b> (the <b>Care of the Dying pathway</b> ) e.g. COPD and metastatic lung cancer) >> then the agitation or restlessness is best treated with <b>Midazolam SC</b> .
--

## Anaphylaxis

Common identified causes of anaphylaxis:

- Food (e.g. Nuts) - the most common cause in children
- Drugs
- Venom (e.g. Wasp sting)

Anaphylaxis may be defined as a severe, life-threatening, generalised or systemic hypersensitivity reaction.

Anaphylaxis is one of the few times when you would not have time to look up the dose of a medication.

The Resuscitation Council guidelines on anaphylaxis have recently been updated.

**Adrenaline IM or SC** is by far the most important drug in anaphylaxis and should be given **as soon as possible**.

The Resuscitation Council guidelines **only** recommend giving **adrenaline intramuscularly**, regardless of whether the patient has IV access or not.

Adrenaline **can be repeated every 5 minutes** if necessary.

The best site for **IM** injection is the **anterolateral aspect of the middle third of the thigh**.

The recommended doses for adrenaline, hydrocortisone and chlorphenamine are as follows:

	Adrenaline (1 in 1000)	Hydrocortisone	Chlorphenamine
<b>&lt; 6 months</b>	150 mcg (0.15ml)	25 mg	250 mcg/kg
<b>6 months - 6 years</b>	150 mcg (0.15ml)	50 mg	2.5 mg
<b>6-12 years</b>	300 mcg (0.3ml)	100 mg	5 mg
<b>Adult and child &gt; 12 yrs.</b>	500 mcg ( <u>0.5ml</u> )	<u>200 mg</u>	<u>10 mg</u>

**Anaphylaxis >>> Serum mast cell Tryptase** levels **rise** following an acute episode within 1-2 hours and may remain elevated for up to 12 hours following an acute episode of anaphylaxis. (**NOT** IgE, plasma histamine nor Basophil count).

**Mast cell tryptase** is the preferred measure test for mast cell degranulation.

Current UK resuscitation guidelines suggest **adrenaline only if** there is:

- 1) **Stridor**
- 2) **Wheeze**
- 3) **Respiratory distress**, or
- 4) **Clinical evidence of shock.**

### Adrenaline

Adrenaline is a sympathomimetic amine with both alpha and beta adrenergic stimulating properties.

Indications:

- Anaphylaxis
- Cardiac arrest

Recommend Adult Life Support (ALS) adrenaline doses:

- Anaphylaxis: **0.5ml 1:1,000 IM**
- Cardiac arrest: **1ml of 1:1000 IV or 10ml 1:10,000 IV**

10ml of the 1:10,000 preparation contains 1mg of adrenaline.

Management of accidental injection: **Local infiltration of Phentolamine.**

Phentolamine, a **short acting alpha blocker**, may be used in this situation. It is normally used mainly to control blood pressure during surgical resection of Pheochromocytoma.

Adrenaline induced ischaemia >>> ttt **Local infiltration with Phentolamine**

### Antihistamines

Antihistamines (H<sub>1</sub> inhibitors) are of value in the treatment of allergic rhinitis and urticaria.

Example of sedating antihistamines: Chlorpheniramine

As well as being sedating these antihistamines have some Antimuscarinic properties (e.g. urinary retention, dry mouth).

Examples of non-sedating antihistamines:

- **Loratidine**
- Cetirizine

Of the non-sedating antihistamines there is some evidence that cetirizine may cause more drowsiness than other drugs in the class.

### **Combined oral contraceptive pill: contraindications**

The decision of whether to start a women on the combined oral contraceptive pill is now guided by the UK Medical Eligibility Criteria (**UKMEC**).

This scale categorises the potential cautions and contraindications according to a four point scale, as detailed below:

- **UKMEC 1:** a condition for which there is no restriction for the use of the contraceptive method
- **UKMEC 2:** advantages generally outweigh the disadvantages
- **UKMEC 3:** disadvantages generally outweigh the advantages
- **UKMEC 4:** represents an unacceptable health risk

### **Examples of UKMEC 3 conditions include: (= Relative contraindications):**

- 1) More than 35 years old and smoking less than 15 cigarettes/day
- 2) BMI > 35 kg/m<sup>2</sup>
- 3) Migraine without aura and more than 35 years old
- 4) Family history of thromboembolic disease in 1st degree relatives < 45yrs
- 5) Controlled hypertension
- 6) Immobility e.g. wheel chair use
- 7) Breast feeding 6 weeks - 6 months postpartum

### **Examples of UKMEC 4 conditions include: (= Absolute contraindications):**

- 1) More than 35 years old and smoking more than 15 cigarettes/day
- 2) Migraine with aura
- 3) History of thromboembolic disease or thrombogenic mutation

- 4) History of stroke or ischaemic heart disease
- 5) Breast feeding < 6 weeks post-partum
- 6) Uncontrolled hypertension
- 7) Breast cancer
- 8) Major surgery with prolonged immobilisation

DM diagnosed > 20 y ago is classified as UKMEC 3 or 4 depending on severity.

### Progestogen only pill: advantages/disadvantages

#### Advantages:

- Highly effective (failure rate = 1 per 100 woman years)
- Doesn't interfere with sex
- Contraceptive effects reversible upon stopping
- Can be used whilst breast-feeding
- Can be used in situations where the combined oral contraceptive pill is contraindicated e.g. in smokers > 35 years of age and women with a history of venous thromboembolic disease

#### Disadvantages:

- **Irregular periods:** some users may not have periods whilst others may have irregular or light periods. This is **the most common adverse effect**
- Doesn't protect against sexually transmitted infections.
- Increased incidence of functional ovarian cysts.
- Common side-effects include breast tenderness, weight gain, acne and headaches. It may be associated with a **reduced libido**. These symptoms generally subside after the first few months.

The primary action of the **combined oral contraceptive pill** is **inhibition of ovulation**, although there are also alterations to the cervical mucus and endometrium which may contribute to effectiveness.

In contrast the **progesterone only pill** does not necessarily affect ovulation and its primary mode of action is **on cervical mucus (thicken cervical mucus) and prevent proliferation of the endometrium and implantation**.

**Hormone replacement therapy (HRT):**

HRT involves the use of a **small dose of oestrogen** (combined with a **progestogen in women with a uterus**) to help alleviate menopausal symptoms.

The indications for HRT have changed significantly over the past ten years as the long-term risks became apparent, primarily as a result of the Women's Health Initiative (WHI) study.

Indications:

- 1) **Vasomotor symptoms** such as flushing, insomnia and headaches.
- 2) **Premature menopause**: should be continued until the age of 50 years.
- 3) **Osteoporosis**: but should only be used as second-line treatment.

The main indication of HRT is >>> the control of <b>vasomotor symptoms</b> .
--

The other indications such as reversal of vaginal atrophy and prevention of osteoporosis should be treated with other agents as first-line therapies.

Other benefits include a **reduced incidence of colorectal cancer**.

Side-effects:

- Nausea.
- Breast tenderness.
- Fluid retention and weight gain.

Potential complications:

- 1) Increased risk of **breast cancer**: increased by the addition of a progestogen.
- 2) Increased risk of **endometrial cancer**: **reduced** by the addition of a **progestogen** but not eliminated completely. The BNF states that the additional risk is eliminated if a progestogen is given continuously.
- 3) Increased risk of **venous thromboembolism**: increased by the addition of a progestogen.
- 4) Increased risk of **stroke**
- 5) Increased risk of **IHD** if taken more than 10 years after menopause. (it frequently produces a **rise** in **triglyceride** concentrations).

**So, Combined OCP:**

- ↑ Risk of Breast cancer+ DVT+ Stroke+ IHD.
- ↓ Risk of Endometrial cancer.

Breast cancer:

- In the Women's Health Initiative (WHI) study there was a relative risk of 1.26 at 5 years of developing breast cancer.
- The increased risk relates to duration of use
- Breast cancer incidence is higher in women using combined preparations compared to oestrogen-only preparations.
- The risk of breast cancer begins to decline when HRT is stopped and by 5 years it reaches the same level as in women who have never taken HRT.

### Prescribing in pregnant patients

Very few drugs are known to be completely safe in pregnancy.

The list below largely comprises of those known to be harmful. Some countries have developed a grading system - see the link.

Antibiotics:

- Tetracyclines
- Aminoglycosides
- Sulphonamides and trimethoprim
- Quinolones: the BNF advises to avoid due to arthropathy in some animal studies

Other drugs:

- ACEI & ARBs
- Statins
- Warfarin
- Sulfonylureas
- Retinoids (including topical)
- Cytotoxic agents

<p>The majority of antiepileptics including valproate, carbamazepine and phenytoin are known to be potentially harmful. The decision to stop such treatments however is difficult as uncontrolled epilepsy is also a risk.</p>
--

### Breast feeding: contraindications

The major breastfeeding contraindications tested in exams relate to drugs (see below). Other contraindications of note include:

- Galactosaemia.
- Viral infections - this is controversial with respect to HIV in the developing world. This is because there is such an increased infant mortality and morbidity associated with bottle feeding that some doctors think the benefits outweigh the risk of HIV transmission.

### The following drugs can be given to mothers who are breast feeding:

- Antibiotics: Penicillins, Cephalosporins, Trimethoprim.
- Hypertension: Methyldopa, Hydralazine, Beta-blockers.
- Digoxin.
- Anticoagulants: heparin, warfarin.
- Endocrine: glucocorticoids (avoid high doses), levothyroxine
- Epilepsy: sodium valproate, carbamazepine.
- Asthma: salbutamol, theophyllines.
- Psychiatric drugs: tricyclic antidepressants, antipsychotics (EXCEPT clozapine should be avoided).

### The following drugs should be avoided in breast feeding:

- Antibiotics: Tetracycline, Sulphonamides, Chloramphenicol, Quinolones
- Psychiatric drugs: lithium, benzodiazepines, **clozapine**.
- **Amiodarone**
- **Aspirin**
- Carbimazole
- **Sulphonylureas**
- Cytotoxic drugs

Breast feeding is acceptable with nearly all anti-epileptic drugs taken in normal doses, with the possible exception of barbiturates.

EX: female with breast feeding and UTI >>> ttt: **Trimethoprim**



**Eclampsia**

Eclampsia may be defined as the development of seizures in association pre-eclampsia. To recap, pre-eclampsia is defined as:

- Condition seen **after 20 weeks gestation**
- **Pregnancy-induced hypertension (PIH)**
- **Proteinuria**

**Magnesium sulphate** is used to both **prevent** seizures in patients with severe pre-eclampsia and **treat** seizures once they develop.

Guidelines on its use suggest the following:

- 1) It should be given **once** a decision to deliver has been made.
- 2) In eclampsia an **IV bolus of 4g over 5-10 minutes** should be given followed by an **infusion of 1g / hour**.
- 3) Treatment **should continue for 24 hours after** last seizure or delivery (around 40% of seizures occur post-partum)
- 4) **Urine output, reflexes, respiratory rate and oxygen saturations** should be monitored during treatment.

MgSO<sub>4</sub> IVI >>>> Monitor >>>> UOP+ Reflexes + RR + O<sub>2</sub> Sat %

Other important aspects of treating severe pre-eclampsia/eclampsia include **fluid restriction** to avoid the potentially serious consequences of fluid overload like Pulmonary and cerebral oedema which are important causes of morbidity and mortality in severe pre-eclampsia.

Severe pre-eclampsia >>> **Restrict fluids**

NICE are very clear on this point: '**Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension**'.

**EX: Methyldopa, Hydralazine, Labetalol and Nifedipine.**

### **Smoking Cessation Therapy**

NICE released guidance in 2008 on the management of smoking cessation. General points include:

- Patients should be offered nicotine replacement therapy (**NRT**), **varenicline** or **bupropion** - NICE state that clinicians should not favour one medication over another.
- NRT, varenicline or bupropion should normally be prescribed as part of a commitment to stop smoking **on or before a particular date** (target stop date).
- Prescription of NRT, varenicline or bupropion should be sufficient to last only until 2 weeks after the target stop date. Normally, this will be after 2 weeks of NRT therapy, and 3-4 weeks for varenicline and bupropion, to allow for the different methods of administration and mode of action. Further prescriptions should be given only to people who have demonstrated that their quit attempt is continuing.
- If unsuccessful using NRT, varenicline or bupropion, **do not offer a repeat prescription within 6 months unless** special circumstances have intervened.
- Do not offer NRT, varenicline or bupropion in any combination.
- Studies have shown success in smoking cessation in **20-30%** of patients involved in **Bupropion** studies at **1 year**. (**Bupropion has a greatest chance of quitting**).

#### **Nicotine Replacement Therapy (NRT):**

- Adverse effects include nausea & vomiting, headaches and flu-like symptoms.
- NICE recommend offering a combination of nicotine patches and another form of NRT (such as gum, inhalator, lozenge or nasal spray) to people who show a high level of dependence on nicotine or who have found single forms of NRT inadequate in the past.

#### **Varenicline (Champix ®):**

- A **Nicotinic receptor partial agonist**.
- Should be started 1 week before the patient's target date to stop.
- The recommended course of treatment is 12 weeks (but patients should be monitored regularly and treatment only continued if not smoking).

- Has been shown in studies to be more effective than bupropion.
- **Nausea** is the most common adverse effect. Other common problems include headache, insomnia, abnormal dreams.
- Varenicline should be used with caution in patients with a past history of depression or deliberate self-harm. There are ongoing studies looking at the risk of suicidal behaviour in patients taking varenicline.
- Contraindicated in pregnancy and breast feeding.

### **Bupropion (Zyban ®):**

- A **Norepinephrine and dopamine reuptake inhibitor**, and **Nicotinic antagonist**.
- Should be started 1 to 2 weeks before the patient's target date to stop.
- Small risk of seizures (1 in 1,000)
- Contraindicated in epilepsy.
- Having an eating disorder is a relative contraindication.
- Contraindicated in pregnancy and breast feeding.

### **Pregnant women:**

NICE recommended in 2010 that all pregnant women should be tested for smoking using carbon monoxide CO detectors, partly because *'some women find it difficult to say that they smoke because the pressure not to smoke during pregnancy is so intense.'*

All women who smoke, or have stopped smoking within the last 2 weeks, or those with a CO reading of 7 ppm or above should be referred to NHS Stop Smoking Services.

### **Interventions:**

- The first-line interventions in pregnancy should be cognitive behaviour therapy, motivational interviewing or structured self-help and support from NHS Stop Smoking Services.
- The evidence for the use of NRT in pregnancy is mixed but it is often used if the above measures failure. There is no evidence that it affects the child's birth weight. Pregnant women should remove the patches before going to bed.
- As mentioned above, varenicline and bupropion are contraindicated in pregnancy and breast feeding.

**Aspirin**

Aspirin works by blocking the action of both cyclooxygenase-1 and 2.

Cyclooxygenase is responsible for prostaglandin, prostacyclin and thromboxane synthesis.

The blocking of thromboxane A<sub>2</sub> formation in platelets reduces the ability of platelets to aggregate which has led to the widespread use of low-dose aspirin in cardiovascular disease.

Until recent guidelines changed all patients with established cardiovascular disease took aspirin if there was no contraindication. Following the 2010 technology appraisal of clopidogrel this is no longer the case\*.

Two recent trials (the Aspirin for Asymptomatic Atherosclerosis and the Antithrombotic Trialists Collaboration) have cast doubt on the use of aspirin in primary prevention of cardiovascular disease. Guidelines have not yet changed to reflect this. However the Medicines and Healthcare products Regulatory Agency (MHRA) issued a drug safety update in January 2010 reminding prescribers that aspirin is not licensed for primary prevention.

**What should receive aspirin according to the current guidelines?**

- 1) All people with established cardiovascular disease (Stroke, TIA, IHD, PVD).
- 2) All people aged  $\geq 50$  years with a 10- year cardiovascular risk  $\geq 20\%$ .
- 3) All people with DM type I or II who are  $\geq 50$  years old or who have DM  $\geq 10$  years, taking ttt for HTN or evidence of target organ damage.
- 4) All people with target organ damage from HTN.

Potentiates:

- Oral hypoglycaemics
- Warfarin
- Steroids

\*NICE now recommend clopidogrel first-line following an ischaemic stroke and for peripheral arterial disease. For TIAs the situation is more complex. Recent Royal College of Physician (RCP) guidelines support the use of clopidogrel in TIAs. However the older NICE guidelines still recommend aspirin + dipyridamole - a position the RCP state is 'illogical'.

**Aspirin** can be **continued normally** if patient is going for **dental** procedure.

**Salicylate overdose**

A key concept for the exam is to understand that salicylate overdose leads to a **mixed respiratory alkalosis and metabolic acidosis**.

**Early** stimulation of the respiratory centre leads to a **respiratory alkalosis** whilst **later** the direct acid effects of salicylates (combined with acute renal failure) may lead to a **metabolic acidosis**.

In children metabolic acidosis tends to predominate.

**Features:**

- Hyperventilation (centrally stimulates respiration).
- **Sweating** and **pyrexia**: as salicylates cause the **uncoupling of oxidative phosphorylation** leading to ↓ **ATP production**, ↑ oxygen consumption and ↑ CO<sub>2</sub> and heat production.
- Nausea/vomiting, occasionally haematemesis.
- Hyperglycaemia and hypoglycaemia.
- **Tinnitus**.
- Pancreatitis
- ARF
- Lethargy.
- Encephalopathy and Seizures.
- Coma.

**Treatment:**

- 1) General: (ABC and **multiple-dose activated charcoal** used be given even up to 12 hrs after overdose ingestion, as there is decreased gastric emptying with salicylates. Although most UK guidelines only recommend its use within the first hour of salicylate ingestion).
- 2) Urinary alkalinization to raise PH of urine from 5 to 8 by **IV NaHCO<sub>3</sub>**, will increase the excretion of the acid 10-fold: It is now rarely used, it is contraindicated in cerebral and pulmonary oedema with most units now proceeding straight to haemodialysis in cases of severe poisoning. There is no value in forced diuresis.
- 3) **Haemodialysis**.

**Indications for haemodialysis in salicylate overdose:**

- 1) **Serum concentration > 700 mg/dl** (5 mmol/litre)
- 2) Acute renal failure
- 3) Metabolic acidosis resistant to treatment
- 4) Pulmonary oedema
- 5) Neurological impairment: (Seizures, Coma or hallucinations)

The **mixed** respiratory alkalosis and metabolic acidosis (**normal or high pH**) in a sweaty, confused patient point towards salicylate overdose. The development of pulmonary oedema suggests severe poisoning and is an indication for haemodialysis

**Paracetamol overdose: management**

Paracetamol can cause liver failure even at relatively low doses (over 7 grams).

A dose of more than 150 mg/kg is considered to be toxic and toxicity occurs at a lower concentration if the patient is thought to be in high risk group.

**Management:**

The following is based on 2012 Commission on Human Medicines (CHM) review of paracetamol overdose management.

The big change in these guidelines was the removal of the 'high-risk' treatment line on the normogram. **All patients are therefore treated the same regardless of risk factors for hepatotoxicity.**

The National Poisons Information Service/TOXBASE should always be consulted for situations outside of the normal parameters.

Paracetamol levels should be carried out at 4 hours not earlier than that.

**Acetylcysteine IVI (Parvolex ®) should be given if:**

- 1) There is **a staggered overdose** (an overdose is considered staggered if all the tablets were not taken within 1 hour); or
- 2) There is **doubt over the time of paracetamol ingestion, regardless** of the plasma paracetamol concentration; or
- 3) **The plasma paracetamol concentration is on or above a single treatment line** joining points of **100 mg/L at 4 hours** and **15 mg/L at 15 hours, regardless** of risk factors of hepatotoxicity.

**Acetylcysteine IVI is now infused over 1 hour** (rather than the previous 15 minutes) to reduce the number of adverse effects.

**Adverse reactions to IV infusion** are seen in about **15%** of individuals in the form of **facial flushing, pruritis** and **rash**.

**TTT** of this adverse reactions is: **stop the IV infusion for a short period**, give **anti-histaminic** and then **re-start the IV infusion at half rate**.

The benefit of NAC is maximum **as long as it is given within 8 hours** of ingestion. Its benefit **extends up to 24 - 36 hours** following ingestion.

The **liver normally conjugates paracetamol** with **glucuronic acid/sulphate** which are then excreted in the urine.

In an **overdose** the **conjugation system becomes saturated** leading to oxidation by P450 mixed function oxidases\*. This produces a **toxic metabolite (N-acetyl-B-benzoquinone imine) (NABQI)** and the drug is then **conjugated with glutathione**.

Normally **glutathione** acts as a defence mechanism by **conjugating** with the **toxin** forming **the non-toxic mercapturic acid**.

If glutathione stores run-out, the toxin forms covalent bonds with cell proteins, denaturing them and leading to cell death. This occurs not only in **hepatocytes** but also in the **renal tubules**.

**N-acetyl cysteine** and **methionine** replenish glutathione stores in the liver so used in the management of paracetamol overdose as it is a **precursor of glutathione** and hence can **increase hepatic glutathione production**.

**Methionine orally** can be used in patients allergic to NAC.

Renal damage may occur by the same way, owing to renal P450 metabolism.

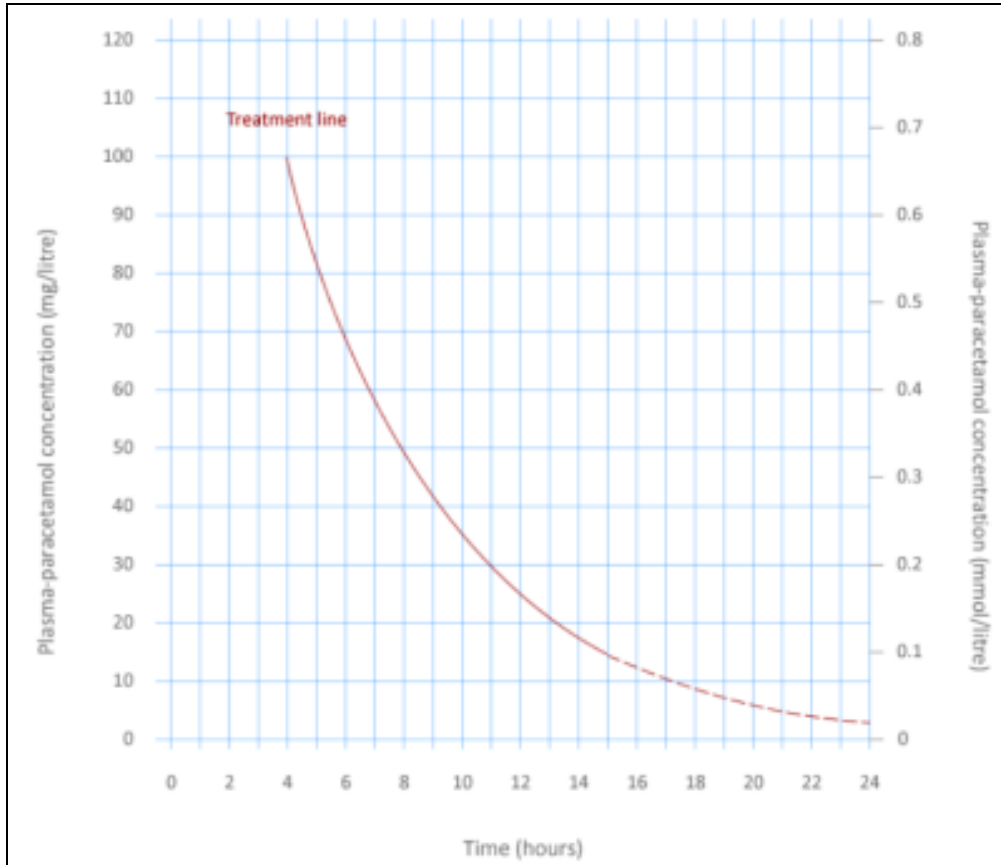
\*this explains why there is a lower threshold for treating patients who take P450 inducing medications e.g. Rifampicin or Phenytoin or Carbamazepine.

The following patients are at ↑ risk of developing hepatotoxicity following a paracetamol overdose:

- 1) **Anorexia nervosa (↓ glutathione stores)**.
- 2) **Alcoholics**.
- 3) P450 enzyme **inducers** like: Rifampicin, Phenytoin, St John's Wort or Carbamazepine.
- 4) **HIV**.

It is true that tobacco smoking induces CYP1A2 (one of the P450 enzymes). However, it is **not** currently included in the list of high-risk situations.

It is unusual to see severe hypotension in paracetamol overdose but is feasible in a **massive overdose** and usually associated with **lactic acidosis** so **first immediate** step in the management is **IV fluids NOT NAC IV**.



**King's College Hospital criteria for liver transplantation (paracetamol-induced acute liver failure):**

**Arterial pH < 7.3, 24 hours after ingestion**

**OR arterial lactate > 3 mmol/L after adequate fluid resuscitation.**

**OR ALL 3 of the following occur in a 24 hr period:**

- **Prothrombin time > 100 seconds (INR > 6.5).**
- **Creatinine > 300 µmol/l.**
- **Grade III or IV encephalopathy.**

**INR** as an indicator of hepatic synthetic function is **the best marker of severity** of paracetamol overdose at this stage.



**INR >2.0** at or before 48 hours or **>3.5** at or before 72 hours should prompt referral to a specialist unit.

Peak elevation occurs around 72-96 hours.

Serum **bilirubin** > 300 µmol/L is part of the selection criteria for liver transplantation in **non-paracetamol** induced acute liver failure.

**King's College Hospital criteria for liver transplantation (in non-paracetamol related liver failure):** (like food e.g. mushroom)

**INR greater than 6.5; OR**

**Three of the following 5 criteria:**

- 1) Patient **age** of less than **11** or greater than **40**.
- 2) Serum **bilirubin** greater than **300** Mmol/L.
- 3) **Time** from onset of jaundice to the development of coma **> 7 days**.
- 4) **INR** greater than **3.5**
- 5) **Drug toxicity, regardless** whether it was the cause of the acute liver failure.

### **Reye's syndrome**

It is the **rarely** occurring **triad** of **encephalopathy**, **fatty liver degeneration** and **elevated transaminases** during a **post-infectious periods**.

It occurs predominantly in patients **under the age of 18 years** and may commonly **follow influenza or varicella infection**.

Case **fatality** rate is **very high** at between **25-50% of patients**.

The key factor in avoiding the syndrome is **the cessation of aspirin use in children**.

Unfortunately there is **no** specific antidote and ttt is supportive, a key factor being recognition and ttt of raised intracranial pressure.

**EX:** 16 years girl has **chicken pox** from nursery contact and has received cold preparation containing **aspirin** & paracetamol then she developed persistent **vomiting, confusion**, generalized tonic-clonic **seizures**, hepatomegaly, ↑ **ALT** 570, and ↑ **AST** 460, ↑ **Bilirubin** 85 Mmol/L >>> **Reye's syndrome**.

**Cyanide poisoning**

Cyanide may be used in insecticides, photograph development, fire/ burning of polyurethane foams in factory or house (fireman) and the production of certain metals.

Toxicity results from irreversible inhibition of cellular oxidising enzymes (irreversible blocking mitochondrial energy transport).

Cyanide causes the **inhibition** of the enzyme **cytochrome oxidase C** which is an essential part of the mitochondrial electron transfer chain (ETC). It therefore interferes with the basic process of **cellular respiration**, preventing the formation of ATP and causing rapid cell death.

**Presentation:**

- 'Classical' features: **Brick-red skin**, smell of bitter almonds.
- Acute:
  - Early: hypoxia, hypotension, headache, confusion, chest tightness.
  - Late: pulmonary oedema, cardiovascular collapse, respiratory arrest, apnoea, paralysis and death within few minutes.
- Chronic: ataxia, peripheral neuropathy, dermatitis.

**Management:**

- Supportive measures: 100% oxygen
- Patient should be **intubated and ventilated**.
- Definitive: **Hydroxocobalamin IV (Dicobalt edetate IV: 300 mg over 1 min, which can be repeated 3 times depending on the response)**,
- Alternatives includes: amyl nitrite (inhaled), sodium nitrite (IV), and sodium thiosulfate (IV).

Cyanide poisoning >>> the antidote of choice is <b>Dicobalt edetate IV</b>
--

Mouth to mouth resuscitation should <b>NOT</b> be attempted where there is a suspicion of cyanide exposure, due to risks to the resuscitators.
--

**EX:** Pt at ICU has severe hypertension on **Na Nitroprusside** and he is stable, after a few hours later he, just after the **nursing shift change**, he has become acutely confused, SOB, central chest pain, abdominal pain, vomiting, BP 100/60 mmHg, PH 7.1, metabolic acidosis, widespread ST depression consistent with myocardial ischaemia >>> **Cyanide poisoning** may be due to uncover of Na Nitroprusside so **it degrades in sunlight to form cyanide** >>> TTT: **Dicobalt edetate** 300 mg IV bolus and can be repeated 3 times, **Nitrate** is an alternative potential for cyanide poisoning if edetate is unavailable.

### **Organophosphate insecticide poisoning**

Usually occurs in **farmers** or **gardener**.

Example: **Malathion** and **Parathion**.

One of the effects of organophosphate poisoning is **irreversible inhibition of acetyl cholinesterase**. (**So** ↑ **Ach**).

Features can be predicted by the accumulation of **acetylcholine** (mnemonic = **SLUDGE**):

- 1) **Salivation**
- 2) **Lacrimation**
- 3) **Urination**
- 4) **Defecation/diarrhoea**
- 5) **Gastrointestinal symptoms**
- 6) **Emesis**.
- 7) Cardiovascular: **hypotension, bradycardia**
- 8) Also: **miosis, muscle fasciculation**

Clinical manifestations may be classified into muscarinic, nicotinic and CNS effects, as follow:

- 1) **Muscarinic**: vomiting, diarrhoea, excessive salivation, sweating, severe diaphoresis, abdominal cramps, bronchospasm, miosis, bradycardia.
- 2) **Nicotinic**: muscle fasciculations, tremors, weakness and death is usually caused by respiratory muscles paralysis.
- 3) **CNS**: agitation, seizures, confusion, coma.

BP and pulse may be decrease due to muscarinic effects, or increased due to nicotinic effects.

Management:

- **Atropine IV:** it may reverse the muscarinic effects, but not the nicotinic effects.
- Supportive measures: **intubation and MV**.
- Decontamination of skin and clothes, and reduction of enteral absorption with activated charcoal may be used.
- The role of **Pralidoxime** is a cholinesterase activator, it is a specific antidote that acts to regenerate the enzyme activity at all affected sites – it should be given as soon as possible in addition to atropine.

### **Carbon monoxide (CO) poisoning**

Carbon monoxide has high affinity for haemoglobin and myoglobin resulting in a **left**-shift of the oxygen dissociation curve and **tissue hypoxia**, anaerobic metabolism and lactic acidosis.

There are approximately 50 per year deaths from accidental carbon monoxide poisoning in the UK.

Questions may hint at **badly maintained housing** e.g. student houses (housemate), caravan, (gas heater switched on but no flame).

Features of carbon monoxide toxicity:

- 1) **Headache:** 90% of cases
- 2) Nausea and vomiting: 50%
- 3) Vertigo: 50%
- 4) **Confusion:** 30%
- 5) Subjective weakness: 20%
- 6) Severe toxicity: **flushing: 'pink' skin and mucosae, hyperpyrexia**, arrhythmias, extrapyramidal features, coma, fits, death.
- 7) **Cherry red skin** is a sign of severe toxicity and is usually seen post-mortem.

The single initial investigation that would be most helpful in the management of that patient is >>> Check **COHb (carboxyhaemoglobin) level**,

COHb levels have **prognostic** implications.

Monitoring SPO<sub>2</sub> with a pulse oximetry is unhelpful since it will not distinguish HbO<sub>2</sub> and COHb.

Typical carboxyhaemoglobin (COHb) levels:

- < 3% non-smokers.
- < 10% smokers.
- 10 - 30% symptomatic: headache, vomiting.
- > 30% severe toxicity.
  - **50-60%:** Syncope, tachycardia, tachypnea, fits.
  - **> 60%:** ↑ risk of cardiorespiratory failure and death.

Carbon monoxide poisoning >> most common feature is **headache**

Confusion, pyrexia and pink mucosa >> are typical features of CO poisoning.

Management:

- 1) **100% oxygen** via tight-fitting **non-rebreather face mask** at a flow rate of **10 L/min.**: first action.
- 2) **Hyperbaric oxygen**: it will short the wash-out of COHb, but access and transfer times to a hyperbaric chamber can make this not practical. Of course, it should be considered post the fitting of non-rebreather mask with 100% oxygen.
- 3) If the patient is **comatose**, he should be **intubated and ventilated with 100% oxygen**.

Indications for hyperbaric oxygen:

- 1) **Loss of consciousness at any point**
- 2) **Neurological** signs **other** than headache e.g. extrapyramidal features.
- 3) **Myocardial ischaemia** or **arrhythmia**
- 4) **Pregnancy**

Fits should be controlled by IV diazepam 5-10 mg.

The metabolic acidosis corrects itself when the hypoxia is treated and does not require ttt with IV NaHCO<sub>3</sub>.

**Lead poisoning**

Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of **abdominal pain** and **neurological signs**.

It result from lead **ingestion**, through the **skin absorption** and by **inhalation** as for **painter** or **decorator** who work in **renovation old houses**.

Features:

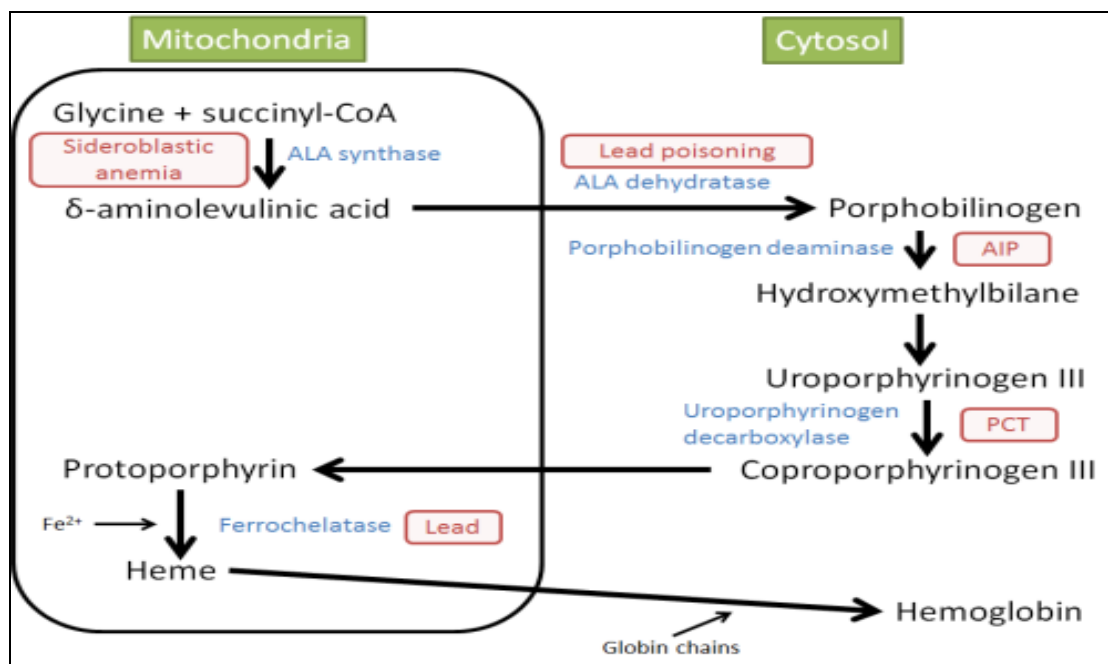
- 1) **Abdominal pain** and **constipation**
- 2) **Peripheral neuropathy** due to **demyelination** (mainly motor)
- 3) Fatigue (**lethargy**).
- 4) **Blue lines on gum margin** (only 20% of adult patients, very rare in children)
- 5) **Hyperkalaemia**: as a result of aldosterone resistance, also known as RTA type 4, because of lead-related renal damage.
- 6) **In severe cases**: Convulsions, Coma, Encephalopathy, and
- 7) **Renal failure** with mild to moderate **proteinuria**.

Investigations:

- 1) The **blood lead level** is usually used for diagnosis. Levels greater than **10 mcg/dl** are considered significant.
- 2) Full blood count: **microcytic anaemia**.
- 3) **Blood film**: **basophilic stippling of RBCs** and clover-leaf morphology.
- 4) ↑ Raised serum and urine levels of **delta amino-laevulinic acid (DALA)** may be seen making it sometimes **difficult** to differentiate from acute intermittent porphyria (AIP).
- 5) ↑ **Urinary Coproporphyrin** is also increased. (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased). But coproporphyrins and porphobilinogens are often normal.

Management - various chelating agents are currently used:

- **D-penicillamine**
- **Dimercaptosuccinic acid (DMSA)**
- Dimercaprol
- Succimer
- EDTA



### Arsenic poisoning

The combination of **mixed sensorimotor polyneuropathy** in the presence of possible exposure to pesticides in a **farmer** would suggest a diagnosis of chronic arsenic poisoning.

The transverse white lines on the finger nails are **Mees' lines**.

NB: Lead poisoning gives a predominantly motor neuropathy.

### Mercury poisoning

Features:

- 1) **Paraesthesia**
- 2) **Visual field defects**
- 3) **Hearing loss**
- 4) **Irritability**
- 5) **RTA** (Renal tubular acidosis)

TTT: Chelation therapy for acute inorganic mercury poisoning can be done with **DMSA** (2,3 dimercapto-1-propanesulfonic acid) which is FDA-approved.

However, several studies found that no clear clinical benefit from DMSA treatment for poisoning due to mercury vapour.

No chelator for methyl-mercury or ethyl-mercury is approved by the FDA. DMSA is the most frequently used for severe methyl-mercury poisoning, as it is given orally, has fewer side effects.

### **Botulinum toxin (Botox)**

As well as the well-publicised cosmetic uses of Botulinum toxin ('Botox') there are also a number of licensed indications:

- 1) **Blepharospasm**
- 2) Hemi facial spasm
- 3) Focal spasticity including cerebral palsy patients, hand and wrist disability associated with stroke
- 4) Spasmodic torticollis
- 5) Severe hyperhidrosis of the axillae
- 6) Achalasia

### **Drugs which act on serotonin receptors (5HT)**

Below is a summary of drugs which are known to act via modulation of the **serotonin (5-HT) system**.

Agonists:

- **Sumatriptan** is a 5-HT<sub>1D</sub> receptor agonist which is used in the **acute** treatment of migraine.
- **Ergotamine** is a partial agonist of 5-HT<sub>1</sub> receptors.

Antagonists:

- **Pizotifen** is a 5-HT<sub>2</sub> receptor antagonist used in the **prophylaxis** of migraine attacks.
- **Methysergide** is another antagonist of the 5-HT<sub>2</sub> receptor but is rarely used due to the risk of retroperitoneal fibrosis.
- **Cyproheptadine** is a 5-HT<sub>2</sub> receptor antagonist which is used to control diarrhoea in patients with carcinoid syndrome.
- **Ondansetron and Granisetron** are a **5-HT<sub>3</sub>** receptor antagonist and is used as an antiemetic. The most common SE is **Constipation**.



It should be noted that 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis.

### Dopamine receptor agonists

Indications:

- 1) **Acromegaly**
- 2) **Parkinson's disease**
- 3) **Prolactinoma/galactorrhoea**
- 4) **Cyclical breast disease**

Currently accepted practice in the management of patients with Parkinson's disease is to delay treatment until the onset of disabling symptoms and then to introduce a dopamine receptor agonist. If the patient is elderly, L-dopa is sometimes used as an initial treatment.

Overview:

- e.g. **Bromocriptine, Cabergoline, Ropinirole**, Apomorphine.
- Ergot-derived dopamine receptor agonists (Bromocriptine, Cabergoline, and Pergolide) have been associated with pulmonary, retroperitoneal and cardiac fibrosis. The Committee on Safety of Medicines advice that an ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored.

Adverse effects:

- 1) **Nausea/vomiting**
- 2) **Postural hypotension**
- 3) **Hallucinations**
- 4) **Daytime somnolence**

**NB:** Pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction.

**Octreotide**

Overview:

- Long-acting analogue of **somatostatin**.
- Somatostatin is released from D cells of pancreas and inhibits the release of growth hormone, glucagon and insulin.

Uses:

- 1) **Acute treatment of variceal haemorrhage**
- 2) **Acromegaly**
- 3) **Carcinoid syndrome**
- 4) Prevent complications **following pancreatic surgery**
- 5) **VIPomas**
- 6) **Refractory diarrhoea**

Adverse effects:

- Gallstones (secondary to biliary stasis).

**Interferon (IFN)**

Interferons (IFN) are cytokines released by the body in response to viral infections and neoplasia.

They are classified according to cellular origin and the type of receptor they bind to.

IFN-alpha and IFN-beta bind to the same type of receptor **type 1 receptors** whilst IFN-gamma binds **only to type 2 receptors**.

**IFN-alpha:**

- Produced by **leucocytes**.
- Antiviral action.
- Useful in hepatitis **B & C**, **Kaposi's sarcoma**, **metastatic renal cell cancer** and **hairy cell leukaemia**.
- Adverse effects include **flu-like symptoms** and **depression**.

**IFN-beta:**

- Produced by **fibroblasts**.
- Antiviral action.
- Reduces the frequency of exacerbations in patients with relapsing-remitting **MS**.

**IFN-gamma:**

- Produced by **T** lymphocytes & **NK** cells.
- **Weaker** antiviral action, more of a role in immunomodulation particularly macrophage activation.
- May be useful in **chronic granulomatous disease** and **osteopetrosis**.

**Motion sickness**

Motion sickness describes the nausea and vomiting which occurs when an apparent discrepancy exists between visually perceived movement and the vestibular systems sense of movement.

Management:

- The BNF recommends **hyoscine** (e.g. transdermal patch) as being the most effective treatment. Use is limited due to side-effects.
- Non-sedating antihistamines such as **cyclizine** or **cinnarizine** are recommended in preference to sedating preparation such as promethazine.

Motion sickness: <b>Hyoscine</b> > <b>cyclizine</b> or <b>cinnarizine</b> > promethazine
--

**Isotretinoin**

Isotretinoin is an oral retinoid used in the treatment of **severe acne**.

It is highly effective in ttt of Acne Vulgaris, it decrease sebum production and sebaceous gland size.

Two-thirds of patients have a long term remission or cure following a course of oral Isotretinoin.

It is a synthetic 13-cis isomer of naturally occurring trans-retinoic acid.

Adverse effects:

- 1) **Highly Teratogenicity:** so females should ideally be using two forms of contraception (e.g. combined oral contraceptive pill and condoms), she should have pre-ttt negative pregnancy test and commit to effective contraception for at least one month pre-ttt and for at least one month after the cessation of ttt.
- 2) **Depression.**
- 3) **Dry** skin, eyes and lips: the most common side-effect of Isotretinoin.
- 4) **Nose bleeds** (caused by dryness of the nasal mucosa).
- 5) Hair thinning.
- 6) Photosensitivity.
- 7) Raised **triglycerides**.
- 8) **Benign intracranial hypertension & papilledema:** Isotretinoin treatment should not be combined with tetracyclines for this reason.
- 9) Isotretinoin has been known to **reduce** ↓ plasma concentration of Carbamazepine.

### Proton pump inhibitors (PPI)

Proton pump inhibitors (PPI) are a group of drugs which profoundly reduce acid secretion in the stomach.

They **irreversibly blocking** the hydrogen/potassium adenosine triphosphatase enzyme system (the **H<sup>+</sup>/K<sup>+</sup> ATPase**) of the gastric **parietal cell**.

PPI can reduce gastric acid secretion by up to **99%**. Acid production resumes following the normal renewal of gastric parietal cells.

Examples include omeprazole and lansoprazole.

### Erythema multiforme (EM)

Features:

- **Target lesions.**
- Initially seen on the back of the hands / feet before spreading to the torso.
- Upper limbs are more commonly affected than the lower limbs.
- Pruritus is occasionally seen and is usually mild.

If symptoms are severe and involve blistering and mucosal involvement the term **Stevens-Johnson syndrome** is used.

Causes:

- Viruses: **HSV (the most common cause)**, Orf (a skin disease of sheep and goats caused by a parapox virus).
- Idiopathic.
- Bacteria: Mycoplasma, Streptococcus.
- Drugs: Penicillin, Sulphonamides, Carbamazepine, Allopurinol, NSAIDs, Oral contraceptive pill, Nevirapine, Griseofulvin.
- Connective tissue disease e.g. SLE.
- Sarcoidosis.
- Malignancy.

### **Toxic epidermal necrolysis (TEN)**

It is a potentially **life-threatening skin disorder** that is most commonly seen secondary to a **drug reaction**.

In which the skin develops a scalded appearance over an extensive area.

Some authors consider TEN to be the severe end of a spectrum of skin disorders which includes **erythema multiforme (EM)** and **Stevens-Johnson syndrome (SJS)**.

Features:

- Systemically unwell e.g. pyrexia, tachycardia
- **Positive Nikolsky's sign**: the epidermis separates with mild lateral pressure.

Drugs known to induce TEN:

- 1) **Penicillins**
- 2) **Sulphonamides**
- 3) **Phenytoin**
- 4) **Allopurinol**
- 5) **Carbamazepine**
- 6) **NSAIDs**

### Management:

- 1) Stop precipitating factor.
- 2) Supportive care, often in ICU.
- 3) **IVIG** (Intravenous immunoglobulin) has been shown to be **effective** and is now commonly used **first-line**.
- 4) Other treatment options include: Immunosuppressive agents (cyclosporine and cyclophosphamide), Plasmapheresis.

### Immunoglobulins: Therapeutics

#### Uses:

- 1) Primary and secondary **immunodeficiency**.
- 2) **ITP** (idiopathic thrombocytopenic purpura) (**NOT TTP**).
- 3) **Myasthenia gravis**
- 4) **GBS**
- 5) **CIDP** (chronic inflammatory demyelinating polyradiculopathy).
- 6) **Kawasaki disease**.
- 7) **TEN**
- 8) **Dermatomyositis**.
- 9) Pneumonitis induced by CMV following transplantation
- 10) ↓ Serum IgG levels following haematopoietic stem cell transplant for malignancy.

#### Basics:

- It is formed from large pool of donors e.g. 5000 persons.
- IgG molecules with a subclass distribution similar to that of normal blood.
- Half-life of 3 weeks.

**Antibiotic guidelines**

The following is based on current BNF guidelines:

**Respiratory system:**

Condition	Recommended treatment
Exacerbations of chronic bronchitis	Amoxicillin or tetracycline or clarithromycin
Uncomplicated community-acquired pneumonia	Amoxicillin (Doxycycline or clarithromycin in penicillin allergic, add flucloxacillin if staphylococci suspected e.g. In influenza)
Pneumonia possibly caused by <u>atypical</u> pathogens	Clarithromycin
Hospital-acquired pneumonia ( <u>HAP</u> )	<ul style="list-style-type: none"> <li>➤ Within 5 days of admission: co-amoxiclav or cefuroxime.</li> <li>➤ More than 5 days after admission: <ul style="list-style-type: none"> <li>○ Piperacillin with tazobactam.</li> <li>○ OR a broad-spectrum cephalosporin (e.g. ceftazidime).</li> <li>○ OR a quinolone (e.g. ciprofloxacin).</li> </ul> </li> </ul>

**Urinary tract:**

Condition	Recommended treatment
Lower urinary tract infection	Trimethoprim or nitrofurantoin. Alternative: amoxicillin or cephalosporin
Acute pyelonephritis	Broad-spectrum cephalosporin or quinolone
Acute prostatitis	Quinolone or trimethoprim

**Skin:**

Condition	Recommended treatment
Impetigo	Topical fusidic acid, oral flucloxacillin or erythromycin if widespread
Cellulitis	Flucloxacillin (clarithromycin or clindomycin if penicillin-allergic)
Erysipelas	Phenoxymethylpenicillin (erythromycin if penicillin-allergic)
<b>Animal or human bite</b>	<b>Co-amoxiclav</b> (Doxycycline + Metronidazole <u>or</u> Clarithromycin + Metronidazole if penicillin-allergic)

**Ear, nose & throat:**

Condition	Recommended treatment
Throat infections	Phenoxymethylpenicillin (erythromycin alone if penicillin-allergic)
Sinusitis	Amoxicillin or doxycycline or erythromycin
Otitis media	Amoxicillin (erythromycin if penicillin-allergic)
Otitis externa*	Flucloxacillin (erythromycin if penicillin-allergic)

**Genital system:**

Condition	Recommended treatment
Gonorrhoea	Cefixime or ciprofloxacin**
<i>Chlamydia</i>	Doxycycline or azithromycin
Pelvic inflammatory disease	Oral ofloxacin + oral metronidazole or intramuscular ceftriaxone + oral doxycycline + oral metronidazole
Syphilis	Benzathine benzylpenicillin or doxycycline or erythromycin
Bacterial vaginosis	Oral or topical metronidazole or topical clindamycin



\* A combined topical antibiotic and corticosteroid is generally used for mild/moderate cases of otitis externa

\*\* There is actually now significant resistance to ciprofloxacin and other guidelines recommend Cefixime 400mg PO (single dose) or ceftriaxone 250mg IM.

### Snake bite

- **Anti-venom** is most effective when given as early as possible, but it must be remembered that there is a 1% chance of having an anaphylactic reaction to this, and so adrenaline should be available during its administration.
- Antivenom is given **IVI over 15 minutes**, and may be repeated after 12 hours if symptoms of systemic envenoming persist.
- The affected area should be immobilized **below** the level of the heart to minimize venous return.
- Any constricting **clothing** should be **removed**.
- Keep the victim **warm**, but **not** to give him warm drinks like caffeine and alcohol.
- **Ice** should **not** be used (as this has been associated with increased necrotic complications).
- Incisions/tourniquets should only be used by an **expert physician**.
- European viper venom antiserum is available and should be considered in the following situations:
  - 1) Persistent hypotension
  - 2) ECG abnormalities.
  - 3) Haemostatic abnormalities.
  - 4) Marked local tissue swelling.

### Drugs cause sensorineural deafness

- **Lasix IV** especially in bolus form, but oral Lasix is unlikely to cause a significant hearing loss.
- **Vancomycin IV**.
- **Erythromycin IV**.

**Drugs causing Gynecomastia:**

- **Oestrogen and Oestrogen-like drugs:**
  - Digoxin
  - OCP
  - DES (Diethyl stilbesterol)
  - Cosmetics or food containing Oestrogen.
- **Drugs which enhance Oestrogen formation:**
  - Gonadotropins.
  - Clomiphene
- **Drugs which inhibit testosterone synthesis or action:**
  - Spironolactone.
  - Ketoconazole.
  - Metronidazole.
  - Cimetidine.
  - Alkylating agents: Cisplatin
- **Drugs whose mechanism of action is unknown:**
  - Methyldopa.
  - ACEI: (Captopril, Lisinopril).
  - CCB (verapamil with long term use)
  - Amiodarone
  - Simvastatin
  - TCA
  - Heroin
  - Marijuana
  - INH
  - Busulphan

**Iron tablets overdose**

C/P:

Circulatory collapse (hypotension), abdominal pain, coffee ground vomiting, black stool.

**Raised bicarbonate** and **low potassium** are more consistent with a metabolic alkalosis secondary to vomiting.

TTT:

- Activated charcoal is NOT used as it is a very poor adsorber to iron.
- **Gastric lavage** is indicated with instillation of Desferrioxamine into the stomach to reduce further iron absorption.

- **Desferrioxamine IV** at rate 15mg/kg/hr is an **initial** ttt of choice and it is important to start with it as early as possible.
- If hypotension/circulatory collapse is not present then it may be given **IM** at the rate of 2 gm every 6-12 hours.
- Haemodialysis
- Plasma exchange

**Iron tablets** are **radiopaque** and thus may be visualised on **plain films** (a number of small radiopaque shadows in the centre of the abdomen) or CT.

### Causes of Hyperpyrexia

- 1) Salicylates
- 2) Ecstasy
- 3) Cocaine
- 4) Neuroleptic malignant syndrome
- 5) Serotonin syndrome
- 6) Thyroid storm
- 7) CO poisoning

### Fever in neutropenia

Assessment of the febrile patient with neutropenia should include:

- Assess for likely **sites** of infection from history, examination and CXR.
- Comprehensive **pan-cultures** of blood, urine, sputum, Hickman line (if present).
- **Barrier nursing** should be instituted if possible.
- If temperature more than 40°C for 4 to 6 hours or if the patient is hypotensive, **blind broad-spectrum antibiotic therapy** should be started (N.B. after taking cultures).
- Antibiotics **should be continued for 2 to 5 days after** the fever has settled and the neutrophil count has recovered.
- If **fever persists after 48 hours** despite antibiotic therapy, **fungal** (Aspergillus, Candida, Pneumocystis) or **viral** (CMV) infection should be considered.
- If infection with Staph aureus is suspected, the addition of **vancomycin** should be considered.

Although preferred antibiotic regimens for neutropenic fever vary from centre to centre, all operate on the same principles.

The aim is to provide **broad-spectrum coverage** that includes cover for **Pseudomonas aeruginosa**.

**Dual therapy regimes** are usually used: a broad-spectrum antibiotic (an antipseudomonal penicillin, carbapenem or ceftazidime) plus an anti-pseudomonal aminoglycoside. (EX: Tazocin + Gentamycin).

(**EX**: Tienam or Meronam or Tazocin **PLUS** Gentamicin or Amikacin ± Vancomycin ± Antifungal ± Anti-viral).

# Infectious Diseases & STDs



### Classification of bacteria

- Gram **Positive cocci** = staphylococci + streptococci (including enterococci).
- Gram **Negative cocci** = **Neisseria meningitidis** + **Neisseria gonorrhoeae**, also **Moraxella**.
- Therefore, only a small list of Gram positive rods (bacilli) need to be memorised to categorise all bacteria - mnemonic = **ABCD L**.
  - **A**ctinomyces.
  - **B**acillus anthracis (anthrax).
  - **C**lostridium.
  - **D**iphtheria: *Corynebacterium diphtheriae*.
  - **L**isteria monocytogenes.
- Remaining organisms are Gram negative rods.

### Incubation periods

Questions may either ask directly about incubation periods or they may be used to provide a clue in a differential diagnosis.

< 1 week	1 - 2 weeks	2 - 3 weeks	>3 weeks
<ul style="list-style-type: none"> <li>• Influenza</li> <li>• Diphtheria</li> <li>• Scarlet fever</li> <li>• Meningococcus</li> </ul>	<ul style="list-style-type: none"> <li>• Measles</li> <li>• Malaria</li> <li>• Typhoid fever</li> <li>• Dengue fever</li> </ul>	<ul style="list-style-type: none"> <li>• Mumps</li> <li>• Rubella</li> <li>• Chickenpox</li> </ul>	<ul style="list-style-type: none"> <li>• Viral hepatitis</li> <li>• HIV</li> <li>• CMV</li> <li>• IMN</li> </ul>

### Antibiotics: mechanisms of action

The lists below summarise the site of action of the commonly used antibiotics:

#### 1) Inhibit cell wall formation:

- 1) Penicillins
- 2) Cephalosporins
- 3) Vancomycin
- 4) Isoniazid (INH)

#### 2) Inhibit protein synthesis:

- 1) Aminoglycosides (cause misreading of mRNA)
- 2) Chloramphenicol
- 3) Macrolides (e.g. erythromycin)
- 4) Tetracyclines (Doxycycline) : protein 30 S ribosome

- 5) Fusidic acid
- 6) Linezolid
- 7) Quinu-pristin & Dalfo-pristin

### **3) Inhibit DNA synthesis:**

- 1) Quinolones (e.g. ciprofloxacin)
- 2) Metronidazole
- 3) Sulphonamides
- 4) Trimethoprim

### **4) Inhibit RNA synthesis:**

- Rifampicin

### **Antibiotics with/without Anti-anaerobic activity**

Antibiotic with **anti-anaerobic** activity:

- Penicillins
- Cephalosporins (except Ceftazidime)
- Erythromycin
- Tetracycline
- Metronidazole

Antibiotic with **NO anti-anaerobic** activity:

- Ceftazidime
- Ciprofloxacin
- Gentamycin

### **Antibiotics: bactericidal vs. bacteriostatic**

<b>Bactericidal</b>	<b>Bacteriostatic</b>
<ul style="list-style-type: none"> <li>➤ Penicillins</li> <li>➤ Cephalosporins</li> <li>➤ Isoniazid</li> <li>➤ Aminoglycosides</li> <li>➤ Quinolones</li> <li>➤ Rifampicin</li> <li>➤ Nitrofurantoin</li> <li>➤ Metronidazole</li> </ul>	<ul style="list-style-type: none"> <li>➤ Macrolides</li> <li>➤ Chloramphenicol</li> <li>➤ Tetracyclines</li> <li>➤ Sulphonamides</li> <li>➤ Trimethoprim</li> <li>➤ Linezolid</li> <li>➤ Dalacin</li> <li>➤ Doxycycline</li> <li>➤ Quinu-pristin &amp; Dalfo-pristin</li> </ul>

### **Linezolid**

It is a type of oxazolidinone antibiotic & has been introduced in recent years.

It inhibits bacterial protein synthesis by stopping formation of the 70s initiation complex and is **bacteriostatic** nature.

Spectrum, highly active against Gram positive organisms including:

- **MRSA** (Methicillin-resistant *Staphylococcus aureus*)
- **VRE** (Vancomycin-resistant enterococcus)
- **GISA** (Glycopeptide Intermediate *Staphylococcus aureus*)

Adverse effects:

- Thrombocytopenia (reversible on stopping).
- Monoamine oxidase MAO inhibitor: avoid tyramine containing foods.

### **Macrolides**

Erythromycin was the first macrolide used clinically.

Newer examples include clarithromycin and azithromycin.

Macrolides act by **inhibiting bacterial protein synthesis**. If pushed to give an answer they are **bacteriostatic** in nature, but in reality this depends on the dose and type of organism being treated.

Adverse effects:

- 1) GIT: Nausea is less common with clarithromycin than erythromycin.
- 2) Cholestatic jaundice: risk may be ↓ if erythromycin stearate is used.
- 3) P450 inhibitor (see below).

Common interactions:

**Statins should be stopped whilst taking a course of macrolides.**

Macrolides inhibit the cytochrome P450 isoenzyme CYP3A4 that metabolises statins. Taking macrolides concurrently with statins significantly increases the risk of statin-induced myopathy and rhabdomyolysis.

**NB:** Statins + Erythromycin/Clarithromycin > an important and common interaction

**NB:** Erythromycin is used in **Gastroparesis** as it has **prokinetic properties** It **Promotes gastric emptying**.



### Quinolones

Quinolones are a group of antibiotics which work by **inhibiting DNA synthesis** and are **bactericidal** in nature. Examples include: Ciprofloxacin and Levofloxacin.

Mechanism of action:

- **Inhibit** topoisomerase II (**DNA gyrase**) and topoisomerase IV.

Adverse effects:

- 1) **Lower seizure threshold** in patients with epilepsy.
- 2) **Tendon damage** (including **rupture**) - the risk is increased in patients also taking steroids.
- 3) **Cartilage damage** has been demonstrated in animal models and for this reason quinolones are generally avoided (but not necessarily contraindicated) in children.

Ciprofloxacin >>> **Tendinopathy**, e.g. rupture tendoachilis

This patient has Tendon damage is a well-documented complication of quinolone therapy. It appears to be an **idiosyncratic** reaction, with the actual median duration of treatment being 8 days before problems occur.

The classical signs of **Achilles tendon** rupture is a sudden, acute onset of pain at the back of the ankle whilst jogging, during which a heard cracking sound.

The BNF advises that **quinolones** 'should be used with **caution** in patients with a history of **epilepsy**, or **conditions that predispose to seizures**'

### Quinupristin & Dalfopristin antibiotics

Overview:

- Injectable streptogramin antibiotic.
- Combination of group A and group B streptogramin.
- **Inhibits bacterial protein synthesis** by blocking t-RNA complexes binding to the ribosome.

Spectrum:

- **Most Gram positive bacteria**

- **Exception: *Enterococcus faecalis*** (not to be confused with *Enterococcus faecium*, which is sensitive to Quinupristin & dalfopristin).

Adverse effects:

- **Thrombophlebitis** (so should give via a **central line**)
- **P450 inhibitor**
- Arthralgia

### Sulfonamides

Antibacterial sulfonamides act as competitive inhibitors of the enzyme DHPS (Dihydropteroate synthetase), an enzyme involved in folate synthesis.

Other uses:

The sulfonamide chemical moiety is also present in other medications that are not antimicrobials such as:

- 1) Loop diuretics: Furosemide, Bumetanide, and Torsemide.
- 2) Thiazide diuretics: Hydrochlorothiazide, Indapamide, Metolazone.
- 3) Sulfonylureas.
- 4) COX-2 inhibitors: Celecoxib.
- 5) Acetazolamide.
- 6) Sulfasalazine.

**Co-trimoxazole:** Sulfonamide antibiotic combination of trimethoprim & sulphamethoxazole (**TMP+SMT**) in the ratio of (**1:5**). Sources differ as to whether it is bactericidal or static.

### Trimethoprim

Mechanism of action of **trimethoprim** >> interferes with DNA synthesis by inhibiting dihydrofolate reductase.

Adverse effects:

- 1) **Myelosuppression**
- 2) **Transient rise in creatinine:** trimethoprim **competitively inhibits the tubular secretion of creatinine** resulting in a temporary increase which reverses upon stopping the drug.

## Diethylcarbamazine

There are two **(Di)** women named **Ethyl** in this **car**: **Di-ethyl-car**. You will notice that there is an elephant between Ethyl and Ethyl.

Used in ttt of **filariasis** (ELEPHANTiasis).



## Staphylococci

Staphylococci are a common type of bacteria which are often found normal commensal organisms but may also cause invasive disease.

Some basic facts include:

- Gram-positive cocci
- Facultative anaerobes
- Produce catalase

The two main types of Staphylococci you need to know about are *Staphylococcus aureus* and *Staphylococcus epidermidis*.

<b>Staphylococcus <u>a</u>ureus</b>	<b>Staphylococcus <u>e</u>pidermidis</b>
<ul style="list-style-type: none"> <li>• Coagulase-positive.</li> <li>• Causes skin infections (e.g. cellulitis), abscesses, osteomyelitis, and toxic shock syndrome (TSS).</li> </ul>	<ul style="list-style-type: none"> <li>• Coagulase-negative.</li> <li>• Cause of <u>central line infections</u> and <u>infective endocarditis</u>.</li> </ul>

Most common organism found in central line infections >>>Staphylococcus epidermidis.

## Streptococci

Streptococci are gram-positive cocci. They may be divided into alpha and beta haemolytic types.

### $\alpha$ -Alpha haemolytic streptococci (Partial haemolysis):

The most important alpha haemolytic *Streptococcus* is ***Streptococcus pneumoniae* (pneumococcus)**.

Pneumococcus is a common cause of pneumonia, meningitis and otitis media.

Another clinical example is ***Streptococcus viridans***.

### $\beta$ -Beta haemolytic streptococci (Complete haemolysis):

These can be subdivided into groups A-H. Only groups A, B & D are important in humans.

#### Group A:

- Most important organism is ***Streptococcus pyogenes***:
- Responsible for erysipelas, impetigo, cellulitis, type 2 necrotizing fasciitis and pharyngitis/tonsillitis.
- Immunological reactions can cause rheumatic fever or post-streptococcal glomerulonephritis.
- Erythrogenic toxins cause scarlet fever.
- Penicillin is the antibiotic of choice for group A streptococcal infection.

#### Group B:

- *Streptococcus agalactiae* may lead to neonatal meningitis and septicaemia.

#### Group D:

- *Enterococcus*.

## Acute epiglottitis

- Acute epiglottitis is rare but serious infection caused by ***Haemophilus influenzae* type B**.
- Prompt recognition and treatment is essential as airway obstruction may develop.

- Epiglottitis generally occurs in **young children** between the ages of 2 and 6 years.
- The incidence of epiglottitis has decreased since the introduction of the Hib vaccine.

Features:

- Rapid onset
- Unwell, toxic child
- Stridor
- Drooling of saliva

### Cellulitis

Cellulitis is a term used to describe an inflammation of the skin and subcutaneous tissues, typically due to infection by **Streptococcus pyogenes** or **Staphylococcus aureus**.

**Features:**

- Commonly occurs on the shins
- Erythema, pain, swelling
- There may be some associated systemic upset such as fever

**Management:** (The BNF recommendations):

- **Flucloxacillin** as first-line treatment for mild/moderate cellulitis.
- **Clindamycin** or **Clarithromycin** is recommend in patients allergic to penicillin.
- Many local protocols now suggest the use of oral clindamycin in patients who have failed to respond to flucloxacillin.
- Severe cellulitis should be treated with IV benzylpenicillin + flucloxacillin.

**EX: Penicillin** is the antibiotic of choice for group A streptococcal infections. The BNF suggests stopping flucloxacillin if streptococcal infection is confirmed by swab in patients with cellulitis, due to the high sensitivity. This should be balanced however with the variable absorption of phenoxymethyl penicillin.

**Staphylococcal toxic shock syndrome (STSS)**

Staphylococcal toxic shock syndrome describes a severe systemic reaction to staphylococcal exotoxins (TSS-1, TSS-2).

It came to prominence in the early 1980's following a series of cases related to infected tampons.

The toxin damages vascular endothelium and triggers release of vasoactive agents from leucocytes and platelets, this increases vascular permeability and contributes to tissue damage.

Staphylococci may be cultured from high vaginal swabs.

Mortality remains approximately 10%.

Although the earliest described cases involved mostly menstruating women using highly absorbent tampons, only 55% of current cases are associated with menstruation. The illness can also occur in children, postmenopausal women, and men.

Risk factors include:

- Recent menstruation
- Recent use of barrier contraceptives such as diaphragms and vaginal sponges
- Vaginal tampon use (especially prolonged)
- Recent childbirth
- Recent surgery, and
- Current *S. aureus* infection.

Centres for Disease Control and Prevention diagnostic criteria:

- 1) **Fever**: temperature > 38.9°C.
- 2) **Hypotension**: systolic blood pressure < 90 mmHg.
- 3) **Diffuse erythematous rash** (resembling sunburn) that peels after 1 to 2 weeks.
- 4) **Desquamation** of rash, especially of the palms and soles.
- 5) Involvement of **3 or more organ systems**: e.g. gastrointestinal (diarrhoea and vomiting), mucous membrane erythema, renal failure, hepatitis, thrombocytopenia, CNS involvement (e.g. confusion).

Blood cultures may be positive for *S. aureus*.

Treatment:

- Removal of the tampons if present.
- Anti-staphylococcal antibiotics e.g. vancomycin or flucloxacillin.

**EX:** A 44-year-old farmer presents to the Emergency Department due to a high temperature and confusion. On examination his pulse is 124 bpm, BP 84/56 mmHg and temperature 39.8°C. He has a generalised erythematous rash which is starting to desquamate on his palms and is also noted to have a paronychia infection of a fingernail on the left hand. The most likely diagnosis >> **SSS**.

**EX:** A 16 years female with manifestations of acute gastroenteritis with high fever 40 C, hypotension BP 70/30 mmHg and rash >>> **TSS**.

### Septic arthritis

Overview:

- Most common organism overall is **Staphylococcus aureus**.
- In young adults who are sexually active **Neisseria gonorrhoeae** should also be considered.

Management:

- Synovial fluid should be obtained before starting treatment
- Intravenous antibiotics which cover Gram-positive cocci are indicated. The BNF currently recommends **flucloxacillin** or clindamycin if penicillin allergic.
- Antibiotic treatment is normally be given for several weeks (BNF states **6-12 weeks**).
- Needle aspiration should be used to decompress the joint.
- Surgical drainage may be needed if frequent needle aspiration is required.

Septic arthritis >>> IV flucloxacillin

### Osteomyelitis

Osteomyelitis describes an infection of the bone.

**Staph. Aureus** is the most common cause, except in patients with sickle-cell anaemia where Salmonella species predominate.

**Predisposing conditions:**

- 1) **DM**
- 2) Sick cell anaemia
- 3) I.V drug user
- 4) Immunosuppression due to either medication or HIV
- 5) Alcohol excess

**Investigations:**

- **MRI** is the imaging modality of choice, with a sensitivity of 90-100%.

**Management:**

- Flucloxacillin for 6 weeks
- Clindamycin if penicillin-allergic

**Necrotising fasciitis**

Necrotising fasciitis is a **surgical emergency** that is difficult to recognise in the early stages.

It can be classified according to the causative organism:

- Type 1 is caused by **mixed aerobes and anaerobes** (often occurs post-surgery in diabetics).
- Type 2 is caused by group A beta- haemolytic **Streptococcus** pyogenes.

Features:

- 1) **Acute onset.**
- 2) **Painful, erythematous** lesion develops.
- 3) Extremely tender over infected tissue.

Management:

- 1) **Urgent surgical debridement.**
- 2) I.V antibiotics (**Clindamycin** and **benzyl penicillin**).

**EX:** A 45-year-old man presents to the Emergency Department due to severe pain in the perineal area over the past 6 hours. On examination the skin is cellulitic, extremely tender and haemorrhagic bullae are seen.



What is the most appropriate management? >>> Urgent surgical debridement.

Surgical referral is the single most important step in the management of necrotising fasciitis. There has been little change in the mortality of necrotising fasciitis since the introduction of antibiotics.

## Anthrax

Anthrax is caused by *Bacillus anthracis*, a Gram positive rod.

It is spread by infected carcasses.

It is also known as Wool sorters' disease.

### **Bacillus anthracis produces a tripartite protein toxin:**

- 1) Protective antigen
- 2) Oedema factor: a bacterial adenylate cyclase which increases cAMP
- 3) Lethal factor: toxic to macrophages

### **Features:**

- Causes **painless black eschar** (cutaneous 'malignant pustule', but **NO pus**).
- Typically painless and non-tender.
- May cause **marked oedema**.
- Anthrax can cause gastrointestinal bleeding.

### **Management:**

- The initial management of **cutaneous anthrax** is **ciprofloxacin**.
- Further ttt is based on microbiological investigations and expert advice.
- **Without antibiotics mortality** is of the order of **20%**, but **with antibiotics**, mortality is **low**, which contrasts with pulmonary anthrax.

**MRSA**

Methicillin-resistant *Staphylococcus aureus* (MRSA) was one of the first organisms which highlighted the dangers of hospital-acquired infections.

**Who should be screened for MRSA?**

- All patients awaiting elective admissions (exceptions include day patients having terminations of pregnancy and ophthalmic surgery. Patients admitted to mental health trusts are also excluded).
- From 2011 all emergency admissions will be screened.

**How should a patient be screened for MRSA?**

- Nasal swab and skin lesions or wounds.
- The swab should be wiped around the inside rim of a patient's nose for 5 seconds.
- The microbiology form must be labelled 'MRSA screen'.

**Suppression of MRSA from a carrier once identified:**

- Nose: mupirocin 2% in white soft paraffin, TID for 5 days.
- Skin: chlorhexidine gluconate, OD for 5 days. Apply all over but particularly to the axilla, groin and perineum.

The following antibiotics are commonly used in the treatment of MRSA infections:

- Vancomycin.
- Teicoplanin (Targocid®).

Some strains may be sensitive to the antibiotics listed below but they should not generally be used alone because resistance may develop:

(i.e. to be used with vancomycin or Teicoplanin):

- Rifampicin
- Macrolides
- Tetracyclines
- Aminoglycosides
- Clindamycin

Relatively new antibiotics such as linezolid, quinupristin/dalfopristin combinations and tigecycline have activity against MRSA but should be reserved for resistant cases.

**N.B:** Whilst tackling MRSA requires a multi-pronged approach the evidence base demonstrates that **hand hygiene** is the single most important step.

**NB:** **Aminoglycosides** may **impair neuromuscular transmission** and should **not** be given to patients with **myasthenia gravis**; large doses given during surgery have been responsible for a transient myasthenic syndrome in patients with normal neuromuscular function (**Aminoglycoside-induced neuromuscular blockade**).

Non-depolarising muscle relaxants (also known as competitive muscle relaxants) compete with acetylcholine for receptor sites at the neuromuscular junction. Non-depolarising muscle relaxants may be divided into the

- Aminosteroid group (ex; pancuronium, vecuronium), and the
- Benzylisoquinolinium group (ex: atracurium).

**EX:** A 23-year-old IV drug user presents with bilateral groin abscesses. After drainage of the abscesses he is started on **IV flucloxacillin and gentamicin**. **Twelve hours later** he complained of diplopia which deteriorated, and also developed dysphagia and muscle weakness and needed ventilatory support. The diagnosis is >>> **Aminoglycoside-induced neuromuscular blockade**.

### **Meningitis: causes**

#### **0 - 3 months:**

- Group B Streptococcus (most common cause in neonates)
- E. coli
- Listeria monocytogenes

#### **3 months - 6 years:**

- Neisseria meningitidis
- Streptococcus pneumoniae
- Haemophilus influenzae

#### **6 years - 60 years:**

- Neisseria meningitidis
- Streptococcus pneumoniae
- Listeria monocytogenes

#### **Immunosuppressed:**

- Listeria monocytogenes

Risk factors for **listeria** meningitis include **older** age and **immunosuppression** (e.g. **prolonged steroid usage for temporal arteritis**).

Meningitis following **neurosurgical procedures** such as V-P shunt operation for hydrocephalus tends to involve a different groups of organisms to normally acquired meningitis. **75%** of all infections involving **VPS** are caused by **staphylococcus epidermis**, next commonest is **staphylococcus aureus** and then **Gram negative bacilli** such as E-Coli, Proteus or Klebsiella.

**Normal CSF:**

Opening pressure	5-18 cm H2O
Glucose	3.3-4.4 mmol
Protein	0.15-0.45 g/l
WBC	< 5/ml

**Meningitis: CSF analysis**

The characteristic cerebrospinal fluid (CSF) findings in meningitis:

	<b>Bacterial</b>	<b>Viral</b>	<b>Tuberculosis</b>
<b>Appearance</b>	Cloudy	Clear/cloudy	Fibrin web
<b>Glucose</b>	Low (< 1/2 plasma)	Normal	Low (< 1/2 plasma)
<b>Protein</b>	High (> 1 g/l)	Normal/raised	High (> 1 g/l)
<b>White cells</b>	10 - 5,000 polymorphs/mm <sup>3</sup>	15 - 1,000 lymphocytes/mm <sup>3</sup>	10 - 1,000 lymphocytes/mm <sup>3</sup>

**NB:** The Ziehl-Neelsen stain is only 20% sensitive in the detection of **tuberculous meningitis** and therefore **PCR** is usually used (sensitivity = **75%**).

**N.B:** Mumps is unusual in being associated with a low glucose level in a proportion of cases.

**N.B:** A low glucose may also be seen in herpes encephalitis

**NB:** A clinical meningitis with an **elevated CSF pressure**, **slightly elevated protein** and **lymphocytosis** is likely to be of **viral** aetiology, particularly in **young** previously **fit** individual.

**EX:** Young female returns from a trip to France with 4-day history of headache, vomiting, fever and neck stiffness >>> **viral meningitis**.

### Meningitis: management

Investigations suggested by NICE:

- CBC, CRP
- Coagulation screen
- Blood culture
- Whole-blood PCR
- Blood glucose
- ABG
- Lumbar puncture **if** no signs of raised intracranial pressure.

### Management:

All patients should be transferred to hospital urgently.

If patients are in a pre-hospital setting (for example a GP surgery) and meningococcal disease is suspected then **intramuscular benzyl penicillin** may be given, as long as this doesn't delay transit to hospital.

Penicillin may cause an **eosinophilic drug reaction**, therefore may be after 3 days of ttt with it the patient develop spikes of new fever with increased eosinophil count in peripheral blood >>> **Stop penicillin and replace with cephalosporin (cefotaxime)**.

Indeed most centres use a cephalosporin as first line therapy because of the small risk of meningococcal resistance to penicillin:

- **< 55 years: Cefotaxime 2 gm/6hrs IVI.**
- **>55 years: Cefotaxime as above + Ampicillin 2 gm/4hrs IVI (for Listeria).**

**BNF recommendations on antibiotics:**

Scenario	BNF recommendation
Initial empirical therapy aged < 3 months.	Cefotaxime IV + amoxicillin
Initial empirical therapy aged 3 months - 50 years.	<b><u>Cefotaxime IV</u></b>
Initial empirical therapy aged > 50 years	Cefotaxime IV + amoxicillin
Meningococcal meningitis	Benzympenicillin IV or cefotaxime
Pneumococcal meningitis	Cefotaxime IV
Meningitis caused by <i>Haemophilus influenzae</i>	Cefotaxime IV
Meningitis caused by Listeria	Amoxicillin IV + gentamicin

If the patient has a history of immediate hypersensitivity reaction to penicillin or to cephalosporins the BNF recommends using **chloramphenicol**.

**Management of contacts:**

- Prophylaxis needs to be offered to household and close contacts of patients affected with meningococcal meningitis.
- **Prophylaxis medication:**
  - **Oral Rifampicin (300 mg: 2 x 2 x 2) or**
  - **Ciprofloxacin 500 mg single oral dose or**
  - **Ceftriaxone single IM** dose may be used and ttt of choice in pregnant women.
- The Health Protection Agency (HPA) guidelines now state that whilst either may be used **ciprofloxacin is the drug of choice** as it is widely available and only requires one dose.
- The risk is highest in the first 7 days but persists for at least 4 weeks.
- **Meningococcal vaccination** should be offered to close contacts when serotype results are available, including booster doses to those who had the vaccine in infancy.

### Meningococcal septicaemia: investigations

Meningococcal septicaemia is a frightening condition for patients, parents and doctors.

It is associated with a high morbidity and mortality unless treated early.

The meningococcal disease is the leading infectious cause of death in early childhood.

A high index of suspicion is therefore needed.

#### Presentation of meningococcal disease:

- 15% - meningitis.
- 25% - septicaemia.
- **60%** - a **combination** of meningitis and septicaemia.

#### Investigations:

- **Blood cultures.**
- **Blood PCR** (It has a sensitivity of over 90%) (It is used if antibiotic was already started).
- Lumbar puncture is usually contraindicated.
- CBC and clotting to assess for DIC.

### Listeria monocytogenes

#### Criteria:

- Listeria is a motile non-spore forming **Gram positive bacillus**.
- It has the unusual ability to multiply at **low** temperatures.
- It is typically spread via contaminated food, typically unpasteurised dairy products (French soft cheese).
- Infection is particularly dangerous to the unborn child where it can lead to miscarriage.

Listeria meningitis should always be considered in patients with meningitis associated with brain stem involvement, and in immunosuppressed patients.

**Features** - can present in a variety of ways:

- 1) Diarrhoea, flu-like illness
- 2) Pneumonia

- 3) CNS infection as meningoencephalitis and even hemiparesis mimicking a stroke.
- 4) Ataxia and seizures

Suspected *Listeria* infection should be investigated by taking blood cultures. CSF may reveal a pleocytosis, with 'tumbling motility' on wet mounts.

**Management:**

- *Listeria* is **sensitive to amoxicillin/ampicillin** (cephalosporins usually inadequate).
- *Listeria* meningitis should be treated with **IV amoxicillin/ampicillin and gentamicin**.

**Lyme disease (Borreliosis)**

It is caused by at least 3 species of bacteria belonging to the genus *Borrelia*.

It is very common in Connecticut where it was given its name when it infected a large group of children in Lyme.

***Borrelia burgdorferi*** sensu stricto is the main cause of Lyme disease in **USA**.

Whereas *Borrelia afzelii* and *Borrelia garinii* cause most European cases.

Around 20% of infections in the UK occur abroad, and **Austria** is a recognised location for Lyme infection.

There are several phases to Lyme disease:

- 1) The **first** being initial headache and neck stiffness.
- 2) The **second** phase normally occurs between 1 to 6 months after infection and presents as meningitis, multiple cranial or peripheral neuropathies, or an acute polyneuropathy resembling Guillain-Barré syndrome.
- 3) Stage **three** of the disease occurs months to years after infection and presents as a chronic myelitis, encephalopathy or demyelinating disorder.

Features:

- **Early:**
  - 1) **Erythema chronicum migrans** (small papule often at site of the tick bite which develops into a larger annular lesion with clear centre, '**bulls-eye**'. Occurs in **70%** of patients).
  - 2) Systemic features (flu like illness, fever, and arthralgia).



- **Later:**

- 1) **CVS:** heart block, prolonged PR interval, myocarditis.
- 2) **Neuro:** cranial nerve palsies (facial Bell's palsy), meningitis.
- 3) **Joints:** Polyarthritis.

Lyme disease can **easily be confused** with **rheumatic fever** and **infective endocarditis**.

Investigation:

- Serology: antibodies to *Borrelia burgdorferi* by ELISA.

Management:

- **Doxycycline for 2-3 weeks** if **early** disease, and it is the drug of choice for those above 8 years and non-pregnant females.
- **Amoxicillin** is an alternative if doxycycline is contraindicated (e.g. pregnancy).
- **Ceftriaxone 2gm IV daily** if **disseminated** disease.
- **Jarisch-Herxheimer reaction** is sometimes seen after initiating therapy: fever, rash, tachycardia after first dose of antibiotic (more commonly seen in syphilis, another spirochaetal disease).

### Leptospirosis (Weil's disease) المجارى ... بول الفئران

Also known as **Weil's disease** (the term Weil's disease is sometimes reserved for the most severe 10% of cases that are associated with jaundice).

Leptospirosis is commonly seen in questions referring to sewage workers, fish farm, farmers, vets or people who work in abattoir.

It is caused by the spirochaete *Leptospira interrogans* (serogroup L icterohaemorrhagiae), classically being spread by contact with infected rat urine.

Weil's disease should always be considered in high-risk patients with hepatorenal failure.

#### **Features:**

- Fever.
- Flu-like symptoms. (**WITHOUT PRODUCTIVE COUGH**)
- Renal failure (seen in **50%** of patients). ↓UOP.

- Jaundice (Liver failure is seen in **only 10%** of patients with leptospirosis).
- Sub-conjunctival haemorrhage
- Thrombocytopenia.
- ↑ CPK
- Headache, may herald the onset of meningitis (meningism).

**Management:**

- High-dose **benzylpenicillin IV** or IV Cephalosporin or **doxycycline**

Leptospirosis give <b>meningism</b> picture with TTT by <b>Doxycycline</b>
--

### Brucellosis

Brucellosis is a zoonosis more common in the Middle East and in farmers.

It is a small slow-growing intracellular organism which histopathologically causes a chronic granulomatous disease.

The Brucella species are small **Gram negative aerobic coccobacilli**

Transmission to humans occurs after occupational exposure or through ingestion of contaminated food products, especially unpasteurised milk products.

Four major species cause infection in humans:

- 1) B. melitensis (sheep),
- 2) B. abortus (cattle),
- 3) B. canis
- 4) B. suis (pigs).

Brucellosis has an incubation period 2 - 6 weeks.

Transmission is through:

- ingestion of unpasteurised milk
- inhalation of infectious aerosols
- direct inoculation through cuts, and
- conjunctival inoculation

Features:

- Non-specific: fever, malaise, paradoxical bradycardia
- Hepatosplenomegaly
- Sacroilitis: spinal tenderness may be seen in up to 55% of cases.

- Leukopenia and thrombocytopenia are often seen.
- Complications: osteomyelitis, infective endocarditis, meningo-encephalitis, orchitis.

Diagnosis:

- **Bone marrow aspiration and culture** is the **gold standard** for diagnosis of brucellosis.
- **Brucella serology** is the best test for diagnosis.
- Blood culture is only positive in 15-70% of cases: Gm negative coccobacilli.
- The Rose Bengal plate test can be used for screening but other tests are required to confirm the diagnosis.

Management:

- Doxycycline and Rifampicin **for 6 weeks**.

### Tuberculosis: screening

The two main tests used for screening in the UK are the **Mantoux (skin) test** and the **interferon-gamma (blood) test**.

Whilst the use of the interferon-gamma test is increasing it is still reserved for specific situations.

The Mantoux test is the main technique used to screen for latent tuberculosis.

One of its uses is for patients who have had close contact with a person known to have tuberculosis.

It is a **cell-mediated** immune response. It measures the **T cell-mediated** immune response to TB antigen. Immune complexes are not involved.

In recent years the **interferon-gamma** blood test has also been introduced. It is used in a number of specific situations such as:

- The Mantoux test is positive or equivocal
- People where a tuberculin test may be falsely negative (see below)

Tuberculin skin tests are an example of **type IV (delayed) hypersensitivity** reactions. These are largely mediated by **interferon- $\gamma$**  secreted by **Th1 cells** which in turn stimulates macrophage activity.

The treatment for **latent tuberculosis** (i.e. Pt with +ve Tuberculin skin Mantoux test and had history of contact to a person proved to have TB) is INH alone for 6 months or dual Rifampicin + INH for 3 months.

**Mantoux test:**

- 0.1 ml of 1:1,000 purified protein derivative (PPD) injected **intradermally** the **left forearm** is typically used.
- Result read **2-3 days later**: Only the **induration**, **not** surrounding erythema, is used in the measurement and the longest diameter is measured in millimetres:

Diameter of induration	Positivity	Interpretation
< 6mm	<b>Negative</b> - no significant hypersensitivity to tuberculin protein	Previously <b>unvaccinated</b> individuals may be given the BCG (within 3 months) provided there are no contraindications.
6 - 15mm	<b>Positive</b> - hypersensitive to tuberculin protein	Should not be given BCG. May be due to <b>previous</b> TB infection or BCG or atypical mycobacteria.
> 15mm	<b>Strongly positive</b> - strongly hypersensitive to tuberculin protein	Suggests <b>tuberculosis</b> infection >> for further investigation (Sputum AFB)

**False negative tests may be caused by:**

- 1) **Miliary TB**
- 2) Sarcoidosis
- 3) Immunosuppression
- 4) HIV
- 5) Viral infections
- 6) Corticosteroids
- 7) Lymphoma
- 8) Very young age (e.g. < 6 months)

**Heaf test:**

The Heaf test was previously used in the UK but has been since been discontinued. It is no longer used in the UK.

The Mantoux test replaced the Heaf test in 2005 in the UK

It involved injection of PPD equivalent to 100,000 units per ml to the skin over the flexor surface of the left forearm. It was then read 3-10 days later.

**Important notes for TB:**

Sputum AFB stain +ve with negative culture >>> Atypical AFB such as *M. avium*

**Primary TB** is usually **asymptomatic**.

**Miliary TB** is the **most likely to occur** in **young children**.

**Primary pulmonary tuberculosis** is often **asymptomatic** consisting of primary complex.

**Cavitation and pleural effusions** are manifestations of **post primary TB**.

The **Ghon focus** is the area of consolidation from cellular infiltration and response to uptake of organisms by macrophages which transform into epithelioid cells and group into granulomata.

Bacilli are transported via **lymphatics early** in the disease process to regional lymph nodes to cause **marked lymphadenopathy**.

Pleural and pericardial infections (which can result in **effusions**) occur **at or shortly after primary infection**.

**Positive tuberculin test** occurs between **3 weeks** and **3 months** after primary infection.

So, **Pleural effusion may occurs before tuberculin skin testing is positive**.

**Non-sputum** producing patients are **non-infectious**.

All forms of pulmonary TB may be treated equally except tuberculous **pleural effusion** which may require **drainage** (with large effusions causing breathlessness) and adjunct corticosteroids to delay reaccumulation.

So lymph node positive disease **does** not requires longer treatment than pulmonary disease.

TB pleural effusion is **small to moderate effusion** rich in **lymphocytes**.

**Pleural effusion AAFB** (Acid Alkali Fast Bacilli) ZN stain are positive in **only 5-10%** (i.e. **it may be TB effusion with negative AFB**) and pleural effusion cultures are

positive in 25-50% of cases over 2-6 weeks and **pleural biopsy culture** is positive in **75%**.

Pleural biopsy histology may demonstrate granulomas, but has a lower sensitivity than culture cannot give bacterial sensitivities.

So the most useful test for the highest pick-up rate for pleural TB diagnosis is >>> **Pleural biopsy culture** (NOT histology or effusion culture or effusion AFB).

**Pleural biopsy culture and histology** give a total diagnostic rate of **90%**.

Pleural effusion **ADA** (Adenosine deaminase) is often raised in TB, but **not specific** as it can be raised in empyema, rheumatoid pleurisy and malignancy.

**EX:** Pt with HIV and pleural effusion with suspected TB >>> **Pleural biopsy culture and histology**.

Pleural fluid volume may increase during anti-TB therapy, **Corticosteroids** are associated with **reduced fluid volume** but have no effect on outcome, and pleural thickening and calcification unfortunately occurs commonly.

The treatment of **TB mediastinal lymphadenitis** is the **same** as **pulmonary TB**.

Length of treatment for other forms are:

- **Bone TB - 9 months**
- **Meningitis - 1 year**
- Drug resistance - minimum of **9 months after** –ve sputum **up to 2 years**.

**Pyrazinamide** have high activity against **intracellular** organisms.

**Streptomycin** has high activity against **extracellular** organisms.

The phenomenon of a **'paradoxical reaction'** during treatment for TB has been recognised for many years. This can result in new lesions, or worsening of existing lesions. It is unpredictable in its timing, and can occur anything from a few days to many months after the start of treatment. Duration and severity is highly variable, and it can be **difficult to differentiate from** treatment failure, drug resistance or a superadded infection. Most cases are recognised in the setting of **lymph node** or **cerebral** disease. LN enlargement is seen in **30%** of cases. Occurrences are usually self-limiting.

**Corticosteroids** are effective in **reducing lymph node enlargement** and inflammation, and hence will help the stridor and breathlessness.

The diagnosis is already known, therefore mediastinoscopy and biopsy will not give any extra information.

EX: Pt with TB of the mediastinal lymph nodes and started anti-TB chemotherapy then developed increasing dyspnoea and stridor dt more LN enlargement at carina >>> TTT: **Corticosteroid**.

**Miliary TB:**

- **15 to 20%** of patients who have **military TB** also have **TB meningitis** at the time of presentation. Conversely 33% of patient with TB meningitis have concomitant miliary TB.
- The **tuberculin test** is often **negative**, so a **negative tuberculin test does not exclude diagnosis of miliary TB**.
- A **chest x ray** may be **normal** in up to **one third** of patients, so **normal CXR does not exclude diagnosis of miliary TB**.
- The classic **millet seed nodules** are **small** measuring about **1-2 mm**.

Mycobacterium **tuberculosis** and Mycobacterium **bovis** are classified as **'typical'** mycobacteria that cause a similar spectrum of disease.

As its name suggests, M. **bovis** also causes disease in **cattle** and the usual source of human infection was from **drinking contaminated milk**; this is now **rare**.

**BCG** (Bacillus Calmette-Guérin) is a **live attenuated** vaccine derived from a **strain of M. bovis**.

BCG is currently used as a form of immunotherapy for treating **bladder cancer**; several cases of disseminated M. bovis infection (systemic 'BCG-it is') have been described as a result of systemic infection following this treatment.

The **non-tuberculous mycobacteria (NTM)**; sometimes referred to as **'atypical'** mycobacteria. They differ from M. tuberculosis in that they are ubiquitous organisms and **have no person-to-person spread**.

Mycobacterium **avium** (also known as Mycobacterium **avium complex [MAC]**, or Mycobacterium avium intracellulare [**MAI**]) causes disseminated infection in patients with advanced **HIV**, typically when the **CD4** count is **less than 50** cells/mm<sup>3</sup>.

This is a disseminated infection that usually causes symptoms of fatigue, weight loss and fevers. **Bone marrow infiltration** is typical and patients are often anaemic and/or **pancytopenic**. The diagnosis is best made from bone marrow **aspiration and culture**. It may also be detected in blood cultures.

**EX:** Pt with **HIV**, fever, loss of weight, **CD 20 cells/mm<sup>3</sup>**, **Pancytopenia**, bone marrow **aspirate** showed acid/alcohol fast bacilli (**AFB**) on light microscopy >>> so Mycobacterium **avium**

M. **fortuitum**, and M. **chelonae** typically present as **painful papular, nodular** or ulcerating **skin** lesions. Both are classified as a rapidly growing mycobacteria and infect immunocompetent individuals. It is a natural environmental organism that has been found in water sources, sewage and dirt.

Other manifestations include osteomyelitis, lymphadenitis, and ocular disease (keratitis and corneal ulceration), usually a result of wound contamination after trauma.

Disseminated disease may be seen in immunosuppressed patients.

Mycobacterium **marinum** infection occurs when contaminated water is exposed to skin that has experienced open trauma. It is an uncommon infection that is usually seen in patients who handle fish or swim in freshwater or saltwater. The skin is the most common site of infection, where it usually produces a solitary indolent granulomatous lesion - the '**fish tank granuloma**'.

### **Tuberculosis: drug therapy**

- The standard therapy for treating **active tuberculosis** is:

#### **Initial phase - first 2 months (RIPE):**

- 1) Rifampicin.
- 2) Isoniazid.
- 3) Pyrazinamide.
- 4) Ethambutol (the 2006 NICE guidelines now recommend giving a 'fourth drug' such as Ethambutol routinely - previously this was only added if drug-resistant tuberculosis was suspected).

#### **Continuation phase - next 4 months:**

- 1) Rifampicin
  - 2) Isoniazid
- The treatment for **latent tuberculosis** (i.e. Pt with +ve Tuberculin skin Mantoux test and had history of contact to a person proved to have TB) is **INH alone for 6 months** or **dual Rifampicin + INH for 3 months**.
- Patients with **meningeal tuberculosis** are treated for a prolonged period (**at least 12 months**) with the addition of **steroids**.
- **Directly observed therapy (DOT)** with a **three times a week** dosing regimen may be indicated in certain groups, including:
- **Homeless** people with **active** tuberculosis.



- Patients who are likely to have poor concordance.
- All prisoners with active or latent tuberculosis.

**N.B:** Streptomycin is used in resistant TB.

**Multi-drug-resistant TB (MDR-TB):**

- As the name suggests is Mycobacterium tuberculosis resistant to 2 or more first line agents, which most commonly are rifampicin and isoniazid.
- There can be mono-resistance to each of the first line agents, but this is not MDR-TB.
- Risk factors for acquiring MDR-TB include previous TB treatment, HIV infection, contact with drug resistant disease and treatment failure.
- Treatment of MDR-TB is complex and time consuming.
- Treatment must be continued for a **minimum of 18 months**, with **at least 9 months of ttt after the patient becomes culture-negative.**
- Initial treatment includes **the use of 5 agents until sputum is negative and then continuation of 3 to which the TB is sensitive to for a minimum of 9 months** but sometimes up to 24 months.
- The minimum overall duration of ttt for MDR-TB once the sputum is negative is **9 months.**

**Tuberculosis: drug side-effects and mechanism of action**

**Rifampicin:**

- Mechanism of action: inhibits bacterial DNA dependent RNA polymerase preventing transcription of DNA into mRNA.
- Potent liver enzyme inducer.
- Hepatitis.
- Orange secretions.
- Flu-like symptoms.

**Isoniazid (INH):**

- Mechanism of action: inhibits mycolic acid synthesis
- Liver enzyme inhibitor
- Hepatitis, agranulocytosis
- Peripheral neuropathy: prevent with pyridoxine (Vitamin **B6**). PN is particularly used in patients with HIV or alcoholics.
- Tonic clonic convulsions: TTT: Diazepam & Vit B6 IV.

Pyridoxine is required as a cofactor in the manufacture of porphyrins for the synthesis of Hb >>> non Fe deficiency microcytic anaemia.

Pyridoxine causes an increase in the peripheral metabolism of Levodopa.

So **patient has both TB and Parkinsonism** with **anaemia** (non Fe def. microcytic anaemia) >>> so ttt of his anaemia with pyridoxine will worsen the Parkinsonism.

**Isoniazid toxicity** should be suspected in any patient with **intractable seizures** and **profound metabolic acidosis** with an elevated anion gap.

Isoniazid monotherapy is used for prevention of active TB in individuals with proven exposure to M. tuberculosis.

**Pyrazinamide:**

- Mechanism of action: converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS) I
- Hyperuricaemia causing gout (There are case reports of Ethambutol-induced gout but it is not listed as a side-effect in the BNF).
- **Hepatitis.**
- **It should not be used in patient with known chronic liver disease**

**Ethambutol:**

- Mechanism of action: inhibits the enzyme arabinosyl transferase which polymerizes arabinose into arabinan.
- Optic neuritis and red-green colour blindness due to optic neuropathy (but not cortical blindness).
- During the early stages of optic neuritis, fundoscopy may will be normal, and patients complain of slowly deteriorating visual acuity and loss of colour differentiation.
- So check visual acuity before and during treatment.
- Recoverability of vision after discontinuation of ethambutol therapy is the subject of some debate.
- Dose adjustment in patients with renal impairment.

**Streptomycin:**

- Vestibular damage → Vertigo and Vomiting
- Cochlear damage → deafness

- Nephrotoxicity
- Angioneurotic oedema

All tuberculosis patients should have pre-treatment LFTs.

If there is no pre-existing liver disease, LFTs are only repeated (and treatment stopped) if fever, malaise, vomiting, jaundice or unexplained deterioration occurs during treatment.

Regular LFTs should be performed in patients with previously known chronic liver disease. If AST/ALT levels rise by **five** times normal/ bilirubin level rises, then **rifampicin/isoniazid/pyrazinamide should be stopped.**

- If the patient is not unwell and/or has non-infectious TB, **no** treatment until LFT returns to normal.
- If clinically unwell or sputum smear is positive within 2 weeks of starting treatment, **consider streptomycin and Ethambutol until LFT returns to normal.**

**Once** LFT is back to normal, **challenge** dosages can be reintroduced sequentially in order of isoniazid, rifampicin and pyrazinamide with **daily** monitoring of patient's condition and LFT.

If there is a further reaction the offending drug should be excluded and a suitable alternative regimen used.

The metabolism of corticosteroids is increased by rifampicin, so patients on long term steroids should have their **dose of steroids increased** when starting antituberculous therapy.

**EX:** Pt with Anti-TB ttt (Rifampicin + INH + Pyrazinamide) for 2 months with elevated AST, ALT, ALP and bilirubin >>> so >>> **STOP ALL treatments.**

### **Leprosy (Hansen's disease) (HD)**

It is a chronic disease caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis*.

Clinical leprosy lies between 2 extremes: Tuberculoid (TT) and Lepromatous (LL), between the 2 ends of the spectrum lies a broad group designated as borderline and sub-classified as borderline tuberculoid (BT), midborderline (BB) and borderline lepromatous (BL).

The disease does not remain static but evolves spontaneously or in response to therapy.

Features:

- Nodular skin lesion.
- Erythematous raised plaque like lesions in arms and legs.

- If left untreated >> progressive leprosy >> permanent damage to the skin, nerves, limbs and eyes.

Diagnosis:

- PCR.
- Nerve conduction study: segmental slowing at the site of nerve entrapment.
- Skin biopsy.

Management:

- **Skin biopsy** and needle test in cold area (ear lobe and elbow).
- **Pauci**-bacillary leprosy (< 5 lesions) >> ttt: Rifampicin+Dapsone for 6 m.
- **Multi**- bacillary leprosy (>5lesions)>>ttt: Rifampicin+Dapsone+Clofazimine for 12 m.

<b>NB:</b> BCG vaccine also give an immunity against leprosy ☺
--

### HIV: the virus

Basics:

- HIV is a **RNA** retrovirus of the lentivirus genus (lentiviruses are characterized by a **long incubation period**).
- Two variants - HIV-1 and HIV-2.
- HIV-2 is more common in West Africa, has a lower transmission rate and is thought to be less pathogenic with a slower progression to AIDS.

Basics structure:

- Spherical in shape with two copies of single-stranded RNA enclosed by a capsid of the viral protein p24.
- A matrix composed of viral protein p17 surrounds the capsid.
- Envelope proteins: gp120 and gp41.
- Pol gene encodes for viral enzymes reverse transcriptase, integrase and HIV protease.

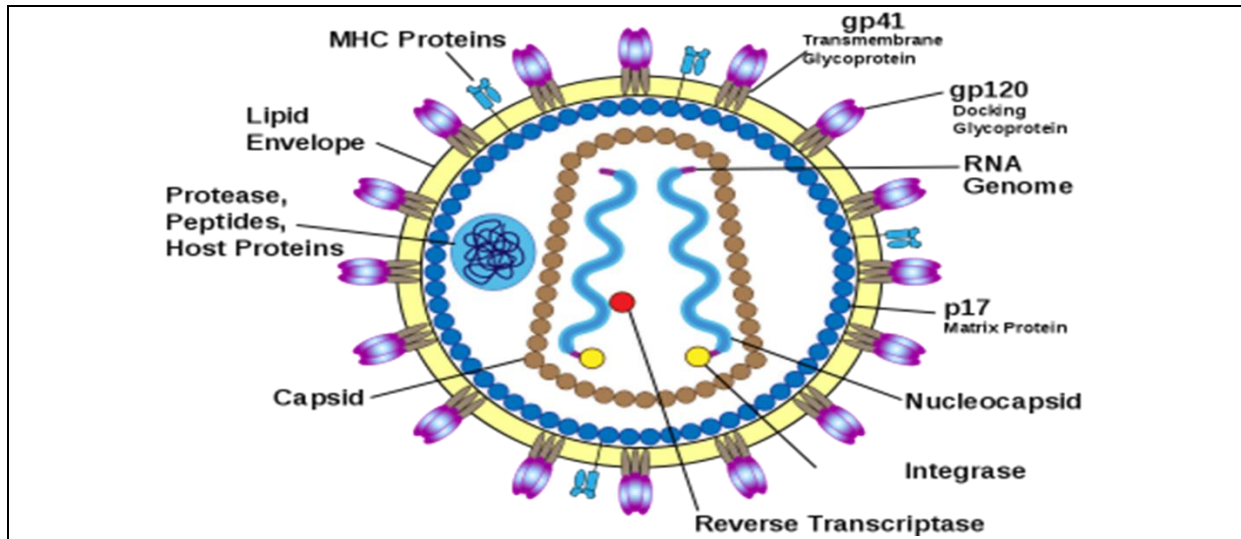
Cell entry:

- HIV can infect **CD4** T cells, **macrophages** and **dendritic** cells.
- Gp120 binds to CD4 and CXCR4 on T cells and CD4 and CCR5 on macrophages.
- Mutations in CCR5 can give immunity to HIV.

Replication:

- After entering a cell the enzyme reverse transcriptase creates dsDNA from the RNA for integration into the host cell's genome.

Regarding targets for anti-HIV drugs. The role of **reverse transcriptase** in HIV infection >>> **Transcribes viral RNA to host DNA.**



#### HIV: Seroconversion (Acute HIV infection)

HIV seroconversion illness is symptomatic in 60-80% of patients and typically presents as a **glandular fever type** illness.

Increased symptomatic severity is associated with poorer long term prognosis.

It typically occurs **2-12 weeks after** primary infection (following exposure to HIV).

Typical symptoms include (4): **fever, pharyngitis, lymphadenopathy** and a widespread **maculopapular rash**.

The illness closely resembles infectious mononucleosis.

NB: Acute Epstein-Barr virus (EBV) is less common in adults as it is usually acquired in teenage years and a diffuse macular rash most often occurs following administration of ampicillin.

Features:

- Fever
- Sore throat

- **Lymphadenopathy**
- **Maculopapular rash**
- **Mucocutaneous ulceration**, Mouth ulcers
- **Malaise**, myalgia, arthralgia
- **Diarrhoea**
- Headache, retro orbital pain
- Neurologic symptoms, e.g. aseptic meningitis, radiculitis, myelitis, **facial** palsy.
- Blood film: **Leukopenia**, **Lymphopenia**, some **atypical lymphocytes** seen and **thrombocytopenia**.

Diagnosis:

- HIV Ab may not be present, so a negative HIV Ab doesn't exclude it.
- **HIV (RNA) PCR** and **P 24 antigen** tests can confirm diagnosis.

**EX: Man** returns from **business** trip abroad with **maculopapular rash** and **flu-like illness** (fever, sore throat), generalised **lymphadenopathy** >>> think **HIV seroconversion**.

**EX:** For questions involving **businessmen** always consider sexually transmitted infections.

**N.B:** The HIV prevalence rate in **Kenya** and **Uganda** is currently around 8%.

### HIV Immunology

The following immunological changes are seen in **progressive HIV**:

- 1) ↓ CD4 count (N > 500/MicroL)
- 2) ↓ NK cell function
- 3) ↓ delayed type IV hypersensitivity responses
- 4) **Increased B2-Microglobulin (IBM)** }
- 5) **Decreased IL-2 production (DIL=DELL)** } **IBM & DELL**
- 6) Polyclonal B-cell activation

Normal CD4 = 300-1300 x 106/L

### HIV: immunisation

The Department of Health 'Green book' on immunisation defers to the British HIV Association for guidelines relating to immunisation of HIV-infected adults.

Vaccines that can be used in all HIV-infected adults	Vaccines that can be used if CD4 > 200	Contraindicated in HIV-infected adults
-Hepatitis A -Hepatitis B -Haemophilus influenzae B (Hib) -Influenza-parenteral -Japanese encephalitis -Meningococcus-MenC -Meningococcus-ACWY I -Pneumococcus-PPV23 -Poliomyelitis-parenteral (IPV) -Rabies -Tetanus-Diphtheria (Td)	-MMR. -Varicella. -Yellow Fever.	- <u>Cholera</u> CVD103-HgR. - <u>Influenza-intranasal</u> . - <u>Oral polio (OPV)</u> . - <u>Tuberculosis (BCG)</u> .

**HIV: Highly Active Anti-Retroviral Therapy (HAART):**

(HAART) involves a combination of at **least three drugs**, typically two nucleoside reverse transcriptase inhibitors (**NRTI**) and either a protease inhibitor (**PI**) or a non-nucleoside reverse transcriptase inhibitor (**NNRTI**).

This combination both decreases viral replication and also reduces the risk of viral resistance emerging.

**Start HAART in HIV when CD4 < 350 \* 10<sup>6</sup>/l**

**Nucleoside analogue reverse transcriptase inhibitors (NRTI):**

- Ex: Zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine, abacavir.
- General NRTI side-effects:
  - NRTI-related cardiomyopathy: due to mitochondrial toxicity (ttt: replace Zidovudine with another one).
  - Peripheral neuropathy
- Zidovudine (AZT) SE: Macrocytosis (Macrocytic anaemia: due to RBCs hypoplasia or aplasia), BM depression, Pt can become transfusion-dependent in severe cases, myopathy up to rhabdomyolysis, black nails, fat redistribution (peripheral fat loss and ↑ abdominal obesity) and insulin resistance.
- Didanosine: pancreatitis.

**Non-nucleoside reverse transcriptase inhibitors (NNRTI):**

- Examples: Nevirapine, Efavirenz.
- Side-effects: P450 enzyme interaction (Nevirapine induces), rashes.
- Nevirapine can cause acute hepatitis and skin rash as a part of hypersensitive reaction

**Protease inhibitors (PI):**

- Examples: Indinavir, Nelfinavir, Ritonavir, Saquinavir, Lopinavir.
- Inhibits a protease needed to make virus able to survive outside the cell.
- Side-effects: **diabetes**, **hyperlipidaemia** (especially ↑**TG**), central obesity, buffalo hump, P450 enzyme inhibition.
- **Indinavir**: SE:
  - Asymptomatic hyperbilirubinaemia,
  - Crystal nephropathy & renal stones: there is drug-drug interactions leading to ↑ indinavir concentration like co-trimoxazole so induce more Crystal nephropathy, ttt: good hydration Normal saline 2-3 L/day.
- **Tenofovir** is associated with acute renal impairment
- **Ritonavir**: a potent inhibitor of the P450 system.
- **Atazanavir** causes isolated hyperbilirubinaemia without elevate aminotransferases (Gilbert like picture).

**HIV: HAART - P450 interaction:**

- Nevirapine (a NNRTI): **induces** P450.
- Protease inhibitors (PI): **inhibits** P450.

**HIV drugs, rule of thumb:**

- NRTIs end in 'ine'
- NNRTIs: Nevirapine, Efavirenz
- Pis: end in 'vir'

**Immune reconstitution syndrome (IRS):**

Some patients after receiving **HAART** will develop an exacerbation of symptoms (more weight loss, drenching night sweats and malaise), signs or radiological manifestation of **TB**.

This has been well described in patients without HIV infection who have a period of depressed immunity, but appears to occur more commonly in HIV-positives patients. The aetiology is unknown but may be due to **HAART-related reconstitution of immunity** leading to abnormal immune response to tubercle antigens released by dead or dying bacilli.

IRS can also occur with other with other infections such as CMV and toxoplasmosis.

**EX:** Pt with HIV started HAART then 3 weeks later he presents extremely unwell with 5 kg weight loss, drenching night sweats and malaise >>> **Immune reconstitution syndrome (IRS)**.



**HIV: Pneumocystis jiroveci pneumonia (=PCP)**

Whilst the organism *Pneumocystis carinii* is now referred to as *Pneumocystis jiroveci*, the term *Pneumocystis carinii* pneumonia (PCP) is still in common use.

- *Pneumocystis jiroveci* is a unicellular eukaryote, generally classified as a fungus but some authorities consider it a protozoa.
- PCP is the most common opportunistic infection in AIDS.
- **All patients with a CD4 count < 200/mm<sup>3</sup> >>> should receive PCP prophylaxis.**

**Features:**

- Dyspnoea
- Dry cough
- Fever
- Very few chest signs
- **Pneumothorax** is a common complication of PCP.
- Extra pulmonary manifestations are rare (1-2% of cases), may cause:
  - HSM
  - Lymphadenopathy
  - Choroid lesions

**Investigation:**

- 1) CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal.
- 2) **Exercise-induced desaturation.**
- 3) Sputum often fails to show PCP.
- 4) **Bronchoalveolar lavage (BAL)** often needed to demonstrate PCP (**silver stain shows characteristic cysts**).

**Management:**

- 1) **Co-trimoxazole IV.**
- 2) **Clindamycin:** can be used in ttt not for prophylaxis.
- 3) **IV pentamidine** in severe cases.
- 4) **± Steroids (high dose Methylprednisolone IV) if hypoxic if PO<sub>2</sub> < 9.3 kPa (< 70 mmHg)** as this is an indicator of severe disease, then steroids reduce risk of respiratory failure by 50% and death by a third.

Patients often deteriorate after starting therapy for PCP as the pneumonitis worsens due to the inflammation associated with dying pneumocysts.

In patients with a  $PO_2 < 70$  mmHg, oral prednisolone is added to reduce the inflammatory effect.

So, ttt is **Co-trimoxazole IV + Prednisolone IV**.

**NB:** Immune Reconstitution Uveitis: Occurs in AIDS in response to immune system recovery, there is granulomatous uveitis that leads to reduced vision and eye discoloration.

### **For prevention of PCP:**

- **Co-trimoxazole orally**, it can't be given as a nebulizer form.
- **Pentamidine nebulizer**.
- **Dapsone**, but can cause haemolysis esp. in G6PD deficiency.

**NB:** With an abnormal CD4 count patients with HIV are at risk for invasive streptococcal infection secondary to streptococcal pneumonia. All patients with HIV should have **routine pneumococcal vaccination**.

**NB:** In patients with well-controlled HIV and a **normal CD4 count pneumonia** can be managed as an outpatient using **CURB scoring** and antimicrobial prescribing guidelines, but with an awareness of the possibility of **drug interactions (like Clarithromycin is a CYP3A4 inhibitor)**.

### **HIV: biliary and pancreatic disease (HIV Cholangiopathy)**

- The most common cause of biliary disease in patients with HIV is **sclerosing cholangitis** due to infections such as Cryptosporidium, CMV and Microsporidia.
- **MRCP/ERCP** for diagnosis.
- **Pancreatitis** in the context of HIV infection may be 2ry to anti-retroviral treatment (especially didanosine) or by opportunistic infections e.g. CMV.

### **HIV: diarrhoea**

Diarrhoea is common in patients with HIV.

This may be due to the effects of the virus itself (HIV enteritis) or opportunistic infections.

Possible causes:

- 1) **Cryptosporidium** + other protozoa (most common)
- 2) Mycobacterium avium intracellulare
- 3) CMV
- 4) Giardia

**Cryptosporidium:**

- It is the most common infective cause of diarrhoea in HIV patients.
- It is an intracellular protozoa and has an incubation period of 7 days.
- Presentation is very variable, ranging from mild to severe diarrhoea.
- **A modified Ziehl-Neelsen stain (acid-fast stain) of the stool** may reveal the **characteristic red rounded oocysts of Cryptosporidium against a blue-green background**. (NOT Cryptosporidium PCR of stool >> it's used only as a research tool).
- Treatment is difficult, with the mainstay of management being **supportive** therapy (Nitazoxanide is licensed in the US for immunocompetent patients).

**Mycobacterium avium intracellulare (MAI):**

- It is an atypical mycobacteria seen with the **CD4 count is below 50**.
- Typical features include fever, sweats, abdominal pain and diarrhoea.
- MAI can present with both **abdominal** and **pulmonary** pathology (pulmonary infiltrate, hilar LN) and with **anaemia**.
- There may be hepatomegaly and deranged LFTs.
- Diagnosis is made by blood cultures and bone marrow examination.
- Management is with Rifampicin, Ethambutol and clarithromycin.
- Patients with a CD4 count below 50 cells/mm<sup>3</sup> should receive MAI inhibitor.

**HIV and pregnancy**

With the increased incidence of HIV infection amongst the heterosexual population there are an increasing number of HIV positive women giving birth in the UK.

In London the incidence may be as high as **0.4% of pregnant women**.

The aim of treating HIV positive women during pregnancy is to minimise harm to both the mother and fetus, and to reduce the chance of vertical transmission.

**Factors which reduce vertical transmission (from 25-30% to 2%):**

- 1) Maternal antiretroviral therapy.
- 2) Mode of delivery (caesarean section).
- 3) Neonatal antiretroviral therapy.
- 4) Infant feeding (bottle feeding).

NICE guidelines recommend offering **HIV screening** to **all pregnant** women.

**1) Antiretroviral therapy:**

- All pregnant women should be offered antiretroviral therapy regardless of whether they were taking it previously.

- If women are not currently taking antiretroviral therapy the RCOG recommend that it is commenced **between 28 and 32 weeks of gestation** and should be continued intrapartum.
- **BHIVA** recommend that antiretroviral therapy may be started at an **earlier** gestation depending upon the individual situation.

## **2) Mode of delivery:**

- **Vaginal** delivery is recommended if viral load is less than 50 copies/ml at 36 weeks, otherwise **caesarean section** is recommended.
- A **Zidovudine IV infusion** should be started 4 hours before beginning the caesarean section.

## **3) Neonatal antiretroviral therapy:**

- Zidovudine is usually administered orally to the neonate if maternal viral load is <50 copies/ml. Otherwise triple ART should be used.
- Therapy should be continued **for 4-6 weeks**.

## **4) Infant feeding:**

- In the UK all women should be advised **not** to breast feed.

## **HIV: Kaposi's sarcoma (KS) (see pic)**

- Caused by **HHV-8** (human herpes virus 8).
- Presents as purple papules or plaques on the skin or mucosa (e.g. gastrointestinal and respiratory tract).
- Skin lesions may later ulcerate.
- Respiratory involvement may cause massive haemoptysis and pleural effusion.
- Pulmonary Kaposi's sarcoma is found in 6-30% of patients with HIV, and is the most common tumour seen.
- In patients with cutaneous Kaposi's, up to 75% have pulmonary Kaposi's tumours on endobronchial biopsy.
- Radiotherapy + resection.

TTT: Retinoid gel may be of value.

**HIV: Skin rash (see pic)**

**Eosinophilic folliculitis** is the **most common** of the popular pruritic disorders in HIV infection.

The underlying pathophysiology is unknown.

It tends to occur when the **CD count is below 300 cell/mm<sup>3</sup>**.

It presents as many excoriated papules and pustules on the chest, back and extensor surface of the arm.

Swabs are usually negative on culture.

On biopsy, a mixed infiltrate of mainly eosinophils with some neutrophils.

It tends to be resistant to most ttt although **HAART** does improve it.

**HIV and Eye**

**CMV retinitis** is the most common cause of eye disease and **blindness** in HIV patients.

CMV retinitis is a slowly progressive disorder; visual loss may occur suddenly as a result of haemorrhage or retinal detachment, or more slowly due to progressive involvement of the macula and optic nerve.

TTT:

- **Foscarnet IV:** trial evidence suggests that viral clearance occurs marginally more quickly in patients treated with Foscarnet and less resistance is seen versus Gancyclovir.
- **Gancyclovir IV 10 mg/kg/day for at least 3 weeks** or until retinitis is quiescent, follow up of **CBC** is recommended to be monitored during Gancyclovir therapy as it is myelosuppressive.
- **Cidofovir IV:** it can be used if both Foscarnet and Gancyclovir are contraindicated or there is a failure to response to one of them.

NB: HIV patient with loss of vision >>> CMV retinitis >>> TTT: Foscarnet IV
---

**HIV: Neuro-complications:**

Generalised	Focal
1) Encephalitis:	1) Toxoplasmosis:
2) Cryptococcus:	2) Lymphoma:
3) PML	3) Tuberculosis:
4) AIDS dementia complex:	

**Generalised neurological disease:**

**1) Encephalitis:**

- May be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

**2) Cryptococcus:**

- Most common fungal infection of CNS.
- Headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit.
- Cryptococcus enters the blood through the lungs so that up to third of patients will report a **pneumonitis** in the weeks preceding systemic cryptococcal infection.
- CSF: high opening pressure, ↑ lymphocytes, **India ink test positive**.
- CT: Meningeal enhancement, cerebral oedema.
- Meningitis is typical presentation but may occasionally cause a space occupying lesion.
- TTT: **Amphotericin B IV (1.5 mg/kg per day) + Flucytosine (5FC) IV (100 mg/kg/d in 4 divided doses) for 2 weeks ± Fluconazole (400 mg/day for 8 weeks).**

**EX:** Any pt with HIV and has meningitis like picture >>>? Cryptococcus meningo-encephalitis >>> Amphotericin B IV + Flucytosine IV.

**3) Progressive multifocal leukoencephalopathy (PML):**

- Widespread demyelination lesions.
- Due to infection of oligodendrocytes by JC papova virus (polyoma DNA virus).
- It occurs almost **exclusively** in **immunosuppressed** individuals such as patients with AIDS, leukaemia or tumours, or those undergoing organ transplantation.
- Before the advent of HIV therapy, up to 4% of patients with AIDS had PML.
- The lesions may occur anywhere but are usually in the cerebral hemispheres, less often in the cerebellum and brainstem and rarely in the spinal cord.
- Almost any neurological sign can be part of the clinical spectrum either motor, sensory or cerebellar signs depending on the white matter areas being affected.
- Symptoms, **subacute (insidious)** onset: visual, motor (hemiparesis), cognitive (Dementia), speech, mental and behavioural changes. Headache and neck stiffness are less common. It progresses faster than the AIDS-dementia complex.
- The PML **progresses rapidly** and the patient is severely disabled, eventually becoming demented, blind and paralyzed and finally there is coma and death.
- CT: single or multiple lesions, **no mass effect**, don't usually enhance and also it may be normal.
- **MRI** is better - high-signal demyelinating multiple white matter lesions are seen.
- CSF is usually normal, but protein may be elevated slightly.
- Brain biopsy has a sensitivity of 74-92% and a specificity of 92-100%.
- **JC virus** can usually be isolated on PCR of CSF in PML and also **JC virus antibodies** may be demonstrated.
- **No specific ttt**, however commencing **HAART** can improve symptoms in some patients although some can deteriorate.

**4) AIDS dementia complex (HIV encephalopathy):**

- Caused by HIV virus itself
- Symptoms: behavioural changes, cognitive dysfunction, motor impairment.

- Typically the presentation is of diffuse subcortical dementia, poor balance, poor co-ordination, ataxic gait, generalised motor weakness diffuse hyperreflexia and patient become incontinent and develop seizure.
- CT: cortical and subcortical **atrophy** with wide sulci

**Focal neurological lesions:**

**1) Toxoplasmosis:**

- Accounts for around **50%** of cerebral lesions in patients with HIV.
- Constitutional symptoms, headache, confusion, drowsiness.
- Cerebral toxoplasmosis is usually cause UMNL rather than lower.
- CT: usually **single or multiple ring enhancing lesions**, **mass** effect may be seen.
- Management: **Sulfadiazine + Pyrimethamine + Folinic acid.**

**EX:** Pt with HIV and TB already on HAART and 4 drug anti-TB, then he develop a grand mal seizure with CT brain revealed a **solitary focal lesion** in the LT internal capsule >>> D.D: cerebral toxoplasma, lymphoma and a tuberculoma, and so **immediate commence with Sulfadiazine + Pyrimethamine**

MRI and toxoplasma serology would be very useful but they are not as urgent as starting toxoplasma ttt.

LP is relatively contraindicated if there is ↑ ICP.

**2) Primary CNS lymphoma:**

- Accounts for around **30%** of cerebral lesions
- Associated with the **EBV** (Epstein-Barr virus)
- CT: single or multiple ring enhancing lesions

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients.

It is clearly important given the vastly different treatment strategies.



Toxoplasmosis	Lymphoma
<ul style="list-style-type: none"> <li>➤ <b>Multiple</b> lesions</li> <li>➤ Ring or nodular enhancement</li> <li>➤ Thallium SPECT <b>negative</b></li> </ul>	<ul style="list-style-type: none"> <li>➤ <b>Single</b> lesion.</li> <li>➤ <b>Solid</b> enhancement.</li> <li>➤ Thallium SPECT <b>positive</b>.</li> </ul>

**NB:** Given the more limited availability of SPECT compared to CT many patients are treated empirically on the basis of scoring systems, for example there is a 90% likelihood of toxoplasmosis if all of the following criteria are met:

- Toxoplasmosis IgG in the serum
- CD4 < 100 and not receiving prophylaxis for toxoplasmosis
- Multiple ring enhancing lesions on CT or MRI

### **3) Tuberculosis:**

- Much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

### **HIV associated nephropathy (HIVAN)**

It is characterised by:

- 1) Low CD4 count
- 2) Nephrotic range proteinuria.
- 3) Normal BP.
- 4) Normal or increased kidney size on US.
- 5) **FSGS** by renal biopsy.

TTT: Initiate **antiretroviral** therapy + ACEI (if not contraindicated).

### **HIV and Addison's disease**

Addison's disease can occur in patients with HIV secondary to **CMV-adrenalitis** which is an immune reconstitution syndrome.

The two causes of Addison's in immunocompromised patient like HIV: are (CMV-Adrenalitis) and TB.

## Antiviral agents

Drug	Mechanism of action	Indications	Adverse effects/toxicity
Acyclovir	Guanosine analogue, it is phosphorylated by <b>thymidine kinase</b> which in turn <b><u>inhibits the viral DNA polymerase.</u></b>	HSV, VZV	Crystalline nephropathy
Ganciclovir	Guanosine analogue, phosphorylated by thymidine kinase which in turn <b><u>inhibits the viral DNA polymerase.</u></b>	CMV	Myelosuppression agranulocytosis
Ribavirin	Guanosine analogue which inhibits inosine monophosphate (IMP) dehydrogenase, <b><u>interferes with the capping of viral mRNA.</u></b>	Chronic HCV, RSV	Haemolytic anaemia

Drug	Mechanism of action	Indications	Adverse effects/toxicity
<b>Amantadine</b>	Inhibits <u>uncoating</u> (M2 protein) of virus in cell. Also releases dopamine from nerve endings.	Influenza, Parkinson's disease	Confusion, ataxia, slurred speech
<b>Oseltamivir (Tamiflu)</b>	<u>Inhibits neuraminidase</u>	Influenza	
<b>Foscarnet</b>	Pyrophosphate analogue which <u>inhibits viral DNA polymerase</u> .	CMV, HSV if not responding to acyclovir.	Nephrotoxicity, hypocalcaemia, hypomagnesaemia, seizures
<b>Interferon-α</b>	Human glycoproteins which <u>inhibit synthesis of mRNA</u> .	Chronic hepatitis B & C, hairy cell leukaemia.	Flu-like symptoms, anorexia, myelosuppression.
<b>Cidofovir</b>	Acyclic nucleoside phosphonate, and is therefore independent of phosphorylation by viral enzymes (compare and contrast with acyclovir/Ganciclovir)	CMV retinitis in HIV.	Nephrotoxicity

### **H1N1 influenza pandemic**

The 2009 H1N1 influenza (swine flu) outbreak was first observed in Mexico in early 2009. In June 2009, the WHO declared the outbreak to be a pandemic.

#### **H1N1:**

The H1N1 virus is a **subtype of the influenza A virus** and the most common cause of flu in humans. The 2009 pandemic was caused by a new strain of the H1N1 virus.

The following groups are particularly at risk:

- 1) Patients with chronic illnesses and those on immunosuppressants
- 2) Pregnant women
- 3) Young children under 5 years old

**Features:** The majority of symptoms are typical of those seen in a flu-like illness:

- Fever greater than 38°C
- Myalgia
- Lethargy
- Headache
- Rhinitis
- Sore throat
- Cough
- Diarrhoea and vomiting

A minority of patients may go on to develop an ARDS (acute respiratory distress syndrome) which may require ventilator support.

**Treatment:** There are 2 main treatments currently available:

#### **1) Oseltamivir (Tamiflu):**

- Oral medication (75 mg cap X 2 x 5).
- In critically ill patients >>> (150 mg x 2 x 10 days).
- A neuraminidase inhibitor which prevents new viral particles from being released by infected cells.
- It may be used in the prophylactic treatment of healthcare workers during flu epidemics. However, long term treatment does run a risk of resistance.
- Common side-effects GIT upset include nausea, vomiting, diarrhoea and headaches.

## 2) Zanamivir (Relenza):

- **Inhaled** medication (**IV** preparations are available for patients who are acutely unwell or cannot use enteral pathway due to vomiting).
- Also a neuraminidase inhibitor.
- May induce bronchospasm in asthmatics.

## **Herpes simplex virus (HSV)**

There are 2 strains of the HSV in humans: HSV-1 and HSV-2.

Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap.

Features:

- Primary infection: may present with a severe gingivostomatitis
- Cold sores
- **Painful** genital ulceration (localised tingling of the genitalia, and shooting pains).

Management:

- Gingivostomatitis: oral acyclovir, chlorhexidine mouthwash.
- Cold sores: topical acyclovir although the evidence base for this is modest.
- Genital herpes:
  - Oral acyclovir.
  - If patient has **frequent exacerbations** more than **6 episodes yearly** may benefit from prophylactic ttt which consist of longer term **oral acyclovir for 3 months**.

## **Genital herpes**

- Genital herpes is most commonly caused by **herpes simplex virus-2 (HSV)**.
- **60%** of **primary** cases are **asymptomatic**.
- **Recurrent attacks** tend to be **shorter** and **less severe**.
- **Viral shedding (transmission)** can occur in the **absence** of lesions.
- **Antiviral** treatment **reduces** the severity of episodes but **is not curative**.
- Topical acyclovir is of **little** benefit.

**HSV II genital ulcers during pregnancy:** ttt **start Acyclovir immediately** at **any** trimester then if further active infection after week 36 then antiviral therapy and a **CS** may be recommended.

### Chickenpox

- Chickenpox is caused by primary infection with varicella zoster virus (VZV).
- Shingles is reactivation of dormant virus in dorsal root ganglion.
- **VZV is the MOST CONTAGIOUS ORGANISM.**

#### **Chickenpox is highly infectious:**

- Spread via the **respiratory** route.
- Can be caught from someone with shingles.
- Infectivity = 4 days before rash, until 5 days after the rash first appeared.
- Incubation period = 10-21 days.

#### **Clinical features (tend to be more severe in older children/adults):**

- Fever initially
- Itchy, rash starting on head/trunk before spreading.
- Initially macular then papular then vesicular.
- Systemic upset is usually mild.

#### **Management is supportive:**

- Keep cool, trim nails.
- Calamine lotion.
- School exclusion: current HPA advice is 5 days from start of skin eruption. They also state 'Traditionally children have been excluded until all lesions are crusted. However, transmission has never been reported beyond the fifth day of the rash.'
- Immunocompromised patients and newborns with peripartum exposure should receive **varicella zoster immunoglobulin (VZIG)**: see later.
- If chickenpox develops then **IV acyclovir** should be considered.

A common complication is secondary bacterial infection of the lesions.

Rare complications include:

- 1) Pneumonia. (Chicken pox pneumonitis)
- 2) Encephalitis (cerebellar involvement may be seen).
- 3) DIC: Disseminated haemorrhagic chickenpox.
- 4) Arthritis, nephritis and pancreatitis may very rarely be seen.

**N.B: Varicella pneumonia:** is the most common and serious complication of chickenpox infection in adults. Auscultation of the chest is often unremarkable, only occasional fine crackles bilaterally. **TTT** of Varicella pneumonia in normal adults >>> **IV acyclovir.**

**N.B: Varicella zoster virus IV immunoglobulin (VZV IVIG):** only recommended as **post exposure prophylaxis** i.e. used for **prevention** of varicella in **at-risk** groups (e.g. Immunocompromised, pregnant women, steroid user), rather than for treatment.

VZV IVIG should be used **within 3 days** of contact/exposure if possible and **not later than 10 days** after exposure. The **varicella antibody (IgG) status** should of course be assessed **firstly**.

So **firstly** check **Varicella IgG Ab**, if negative so **then VZV IVIG**.

### **Chickenpox exposure in pregnancy**

In pregnancy there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome (FVS).

#### **Fetal varicella syndrome (FVS):**

- Risk of FVS following maternal varicella exposure is around 1% if occurs before 20 weeks gestation.
- Studies have shown a very small number of cases occurring between 20-28 weeks gestation and none following 28 weeks.
- Features of FVS include skin scarring, eye defects (microphthalmia), limb hypoplasia, microcephaly and learning disabilities.

#### **Management of chickenpox exposure to a pregnant woman:**

- 1) If there is any doubt about the mother previously having chickenpox **maternal blood should be checked for varicella antibodies (IgM & IgG).**
- 2) If the pregnant woman is not immune to varicella she should be given **varicella zoster immunoglobulin (VZIG) as soon as possible**. RCOG and Green book guidelines suggest VZIG is effective up to 10 days post exposure.
- 3) Consensus guidelines suggest **oral acyclovir** should be given if pregnant women with chickenpox present within 24 hours of onset of the rash.

Chickenpox exposure in pregnancy >>> first step is to check maternal varicella antibodies IgM & IgG. Negative IgG indicates no previous exposure to chickenpox >>>so start ttt: VZIG.

### Ramsay Hunt syndrome

Ramsay Hunt syndrome (**herpes zoster oticus**) (**herpes zoster ophthalmicus**) is caused by the **reactivation** of the **varicella zoster virus (VZV)** in the geniculate ganglion of the **seventh** cranial nerve.

Features:

- 1) **Auricular pain** is often the **first** feature.
- 2) **Facial nerve palsy.**
- 3) **Vesicular rash around the ear** classically seen in the external auditory canal and pinna they may also be seen on the **anterior 2/3rds of the tongue and the soft palate.**
- 4) Vesicles present on the **nasolabial folds** or on the **tip of nose** suggests involvement of the **cornea (Hutchinson sign)**, therefore the most important consideration is **urgent ophthalmological assessment** to reduce the risk of loss of vision.
- 5) Various ophthalmic manifestations may occur: keratitis (within first few days); periorbital and conjunctival oedema (1<sup>st</sup> week); secondary bacterial infection (staphylococci); later scarring of anterior chamber leading to glaucoma and cataract.
- 6) Other features include **vertigo** and **tinnitus**.

Management:

- **Oral acyclovir** and **corticosteroids** are usually given.

### Infectious mononucleosis (IMN) (EBV) (glandular fever) (HHV-4)

Infectious mononucleosis (glandular fever) is caused by the Epstein-Barr virus it is one of the **herpes** viruses: (also known as human herpesvirus 4, **HHV-4**).

It is most common in adolescents and young adults.

#### **Features:**

- Sore throat
- Lymphadenopathy
- Pyrexia
- Malaise, anorexia, headache
- Palatal petechiae



- Splenomegaly - occurs in around 50% of patients and may rarely predispose to splenic rupture
- Hepatitis
- Presence of 50% lymphocytes with at least 10% atypical lymphocytes.
- Haemolytic anaemia secondary to cold agglutins (IgM)
- A maculopapular, pruritic rash develops in around **99%** of patients who take ampicillin/amoxicillin whilst they have infectious mononucleosis.

URTI symptoms + amoxicillin → rash, so? Glandular fever

Atypical lymphocytes in blood film>>>>? Glandular fever

### Diagnosis:

- Heterophil antibody test (**Monospot test**) (**Paul-Bunnell test**).

**Management** is supportive and includes:

- Rest during the early stages, drink plenty of fluid, and avoid alcohol.
- Simple analgesia for any aches or pains.
- Consensus guidance in the UK is to avoid playing contact sports for 8 weeks after having glandular fever to reduce the risk of splenic rupture.

### **Epstein-Barr virus (EBV): associated conditions**

Malignancies associated with EBV infection:

- 1) **Burkitt's** lymphoma (both African and sporadic Burkitt's).
- 2) **Hodgkin's** lymphoma
- 3) **Nasopharyngeal** carcinoma
- 4) **HIV-associated CNS** lymphomas
- 5) **Oral Hairy leukoplakia** (but it is **non-malignant** condition).

**N.B:** Adult T-cell leukaemia is associated with HTLV-1 infection.

### **Burkitt's lymphoma**

- It makes up about 2% of all lymphoma.
- The cells are medium-sized. There is a **very fast growing lymphoma** so presented in a **short space of time**.
- In the **African** variety, it often starts as tumours of the **jaws** or other **facial** bones.
- In the most common types seen in the **USA**, the lymphoma usually started in the **abdomen**, where it forms a large tumour mass.

- It can also spread to the brain and spinal fluid.
- 90% of patients are **men** and the average age is about **30**.
- It is a **fast growing lymphoma**, but **half** of patients are cured by **aggressive chemotherapy**.

**EX:** Male 40 y/o with 5-week history of generalized abdominal pain, nausea, weight loss, fever, night sweats, no diarrhoea, LDH 4000 >>> **Burkitt's lymphoma**. (If long history duration >>> think of TB).

### Oral hairy leukoplakia:

- It is **painless** shaggy **adherent** **white patches** affecting the **lateral borders of the tongue** ± cervical and axillary **lymphadenopathy**.
- Unlike Candida, the lesions is **adherent** and **cannot be scraped off** the tongue.
- It is caused by reactivation of EBV which occurs in patients who are **immunocompromised** like HIV.
- In most cases the diagnosis is **clinical**, but EBV can be demonstrated in epithelial cells with immunohistochemical staining.
- No specific ttt, but **HIV screening** should be done >>> **HART**.

## Measles

### Overview:

- **RNA** paramyxovirus
- Spread by droplets
- Infective from prodrome until 4 days after rash starts
- Incubation period = 10-14 days

### Features:

- Prodrome: irritable, conjunctivitis, fever.
- Koplik spots (before rash): white spots ('grain of salt') on buccal mucosa.
- Rash: starts behind ears then to whole body, discrete maculopapular rash becoming blotchy & confluent.

### Complications:

- **Encephalitis**: typically occurs 1-2 weeks following the onset of the illness)
- **Subacute sclerosing pan-encephalitis**: very rare, may present 5-10 years following the illness

- Giant cell **pneumonia**
- Febrile convulsions
- Keratoconjunctivitis, corneal ulceration
- Diarrhoea
- ↑ incidence of appendicitis
- Myocarditis

N.B: Pancreatitis and infertility may follow mumps infection not measles.

**Management of contacts:**

- If a child not immunized against measles comes into contact with measles then **MMR** should be offered (vaccine-induced measles antibody develops more rapidly than that following natural infection).
- This should be given **within 72 hours**.

**AMS (Atypical Measles Syndrome)**

It occurs in persons who were **incompletely immunised against measles**.

This may occur either because they were given the old killed virus measles vaccine (no longer available) or they were given the attenuated (weakened) live measles vaccine which had been inactivated due to improper storage.

The latter **dose not prevent measles** but causes an alteration in its expression, resulting in AMS.

**Pneumonia** is a common complication and may persist for months.

**Virus isolation, serological** studies, or both may be necessary to confirm the diagnosis.

Rocky Mountain Spotted Fever (RMSF) is a viable differential diagnosis.

**Parvovirus B19 (fifth 5<sup>th</sup> disease) or (slapped cheek syndrome)**

It is a **DNA** virus which causes a variety of clinical presentations.

It was identified in the **1980's** as the cause of **erythema infectiosum**.

Erythema infectiosum (also known as fifth disease or "slapped cheek syndrome").

Features:

- Systemic constitutional symptoms: fever, headache, lethargy.
- Slapped cheek rash spreading to proximal arms and extensor surfaces.

- May be asymptomatic.
- Pancytopenia in immunosuppressed patients.
- **Parvovirus B19-related red cell aplasia** is associated with **HIV >>> anaemia without reticulocytosis** and **BM aspirate** will show **pure red cell aplasia**.
- Infection can be confirmed by IgM serology or PCR.
- **Aplastic crises**: e.g. in **sickle cell disease** (Parvovirus B19 suppresses erythropoiesis for about a week so aplastic anemia is rare unless there is a chronic hemolytic anaemia).
- It is known to cause fetal anaemia, hydrops fetalis (2<sup>nd</sup> trimester) and IUFD.
- Parvovirus B19 infection may account for up to 20% of non-immune cases of **hydrops fetalis**.
- Autopsy studies indicates that highest viral concentration are found in bone marrow and myocardium.

The most common complication associated with fetal slapped cheek infection is >>> **Hydrops fetalis**.

### **Reye's syndrome**

Reye's syndrome is a **severe, progressive encephalopathy** affecting children that is accompanied by **fatty infiltration** of the liver, kidneys and pancreas.

The aetiology of Reye's syndrome is not fully understood although there is a known association with **aspirin** use and a **viral** cause has been postulated.

The peak incidence is **2 years of age**, features include:

- 1) May be history of **preceding viral** illness and/or **aspirin** use.
- 2) **Encephalopathy**: confusion, **seizures**, cerebral oedema, coma.
- 3) **Fatty infiltration** of the liver, kidneys and pancreas.
- 4) **Hypoglycaemia**.

Management is supportive:

Although the prognosis has improved over recent years there is still a mortality rate of 15-25%.

## **Chlamydia**

Chlamydia is **the most prevalent sexually transmitted infection in the UK** and is caused by *Chlamydia trachomatis*, an obligate intracellular pathogen.

Approximately 1 in 10 young women in the UK have Chlamydia.

The incubation period is around 7-21 days, although it should be remembered a large percentage of cases are **asymptomatic** so unfortunately usually the diagnosis is missed.

Non-specific urethritis (**NSU**) is caused by **Chlamydia** in **60%** of cases.

**Azithromycin** and **Doxycycline** are both commonly used in ttt of **NSU**. NSU can be **non-infective** in origin e.g. after a night of heavy alcohol consumption, in men who use antiseptic to clean their urethra or post vigorous sex or masturbation.

The possibility of **pelvic infection** in **young** women of **reproductive** age who complain of **back ache** with no restriction of spinal movement, particularly **chlamydia**, should always be borne in mind especially when with normal urine analysis and elevated CRP.

### **Features:**

- **Asymptomatic** in around 80% of women and 50% of men.
- Women: cervicitis (discharge, bleeding), dysuria.
- Men: urethral discharge, dysuria & acute epididymitis (D.D. Torsion testis).

### **Potential complications:**

- Epididymitis.
- PID (like Endometritis).
- ↑ Incidence of ectopic pregnancies.
- Infertility.
- Reactive arthritis.
- Periappendicitis
- Perihepatitis (Fitz-Hugh-Curtis syndrome).

### **Investigation:**

- Traditional cell culture is no longer widely used
- **Chlamydial Nuclear acid amplification tests (NAATs)** are now rapidly emerging as the investigation of choice with high sensitivity 95%.

- Urine (first void urine sample), vulvovaginal swab or cervical swab may be tested using the NAAT technique.

**Screening:**

- In England the National *Chlamydia* Screening Programme (NCSP) is open to all men and women aged 15-24 years.
- The 2009 SIGN guidelines support this approach, suggesting screening all sexually active patients aged 15-24 years.
- Relies heavily on opportunistic testing.

**Management:**

- **Azithromycin (2gm PO single dose) or Doxycycline (100mg X 2X 7).**
- The 2009 SIGN guidelines suggest azithromycin single oral dose should be used first-line due to potentially poor compliance with a 7 day course of doxycycline.
- Sexual contacts should also be traced and treated if possible.
- **Current UK guidelines** recommend **3** different options in **pregnancy**:
  - **Erythromycin** 500 mg QDS for 7 days or BD for 14 days
  - **Amoxicillin** 500 mg TDS for 7 days
  - **Azithromycin** 1 g stat - the BNF cautions that this should **only** be used **if** there are no alternatives.
- Patient should refrain from intercourse for a period of 7 days.
- Contact partner notification should be encouraged.
- Patients diagnosed with Chlamydia should be offered a choice of provider for initial partner notification - either trained practice nurses with support from GUM, or referral to GUM.
- For men with symptomatic infection all partners from 4 weeks prior to the onset of symptoms should be contacted.
- For women and asymptomatic men all partners from the last 6 months or the most recent sexual partner should be contacted.
- Contacts of confirmed Chlamydia cases should be offered treatment prior to the results of their investigations being known (treat then test).
- A test of cure should be carried out following treatment.

**EX:** A 20-year-old man presents with dysuria and a urethral discharge. Gram staining of the urethral discharge demonstrates neutrophils but no bacteria.

The most likely causative organism >>> **Chlamydia trachomatis**

**Chlamydia psittaci (psittacosis) = parrot disease (parrot fever):**

It is characterized by malaise, fever, myalgia and pneumonia.

Exposure to an ill bird and a rash (Horder's spots) are pathognomonic.

TTT: Erythromycin or tetracycline is the drug of choice.

## Gonorrhoea

Gonorrhoea is caused by the **Gram negative diplococcus** *Neisseria gonorrhoea*. Acute infection can occur on any mucous membrane surface, typically genitourinary but also rectum and pharynx.

The incubation period of gonorrhoea is 2-5 days.

### **Features:**

- Males: urethral discharge, dysuria.
- Females: cervicitis e.g. leading to vaginal discharge.
- Rectal and pharyngeal infection is usually asymptomatic.

Local complications that may develop include urethral strictures, epididymitis and salpingitis (hence may lead to **infertility**). Disseminated infection may occur.

### **Management:**

- Ciprofloxacin 500mg PO used to be the treatment of choice.
- However, there is increased resistance to ciprofloxacin and therefore cephalosporins are now used the treatment of choice for Gonorrhoea.
- Options include **Cefixime 400mg PO (single dose)** or **Ceftriaxone 250mg IM.**

Cephalosporins are now the treatment of choice for Gonorrhoea

**Disseminated gonococcal infection (DGI)** and gonococcal arthritis may also occur, with gonococcal infection being the most common cause of septic arthritis in young adults.

The pathophysiology of DGI is not fully understood but is thought to be due to haematogenous spread from mucosal infection (e.g. asymptomatic genital infection).

Initially there may be a classic **triad** of symptoms: **tenosynovitis, migratory polyarthritis and dermatitis**.

Later complications include septic arthritis, endocarditis and Perihepatitis (Fitz-Hugh-Curtis syndrome).

**Key features of disseminated gonococcal infection (DGI):**

- 1) Tenosynovitis
- 2) Migratory polyarthritis
- 3) Dermatitis (lesions can be maculopapular or vesicular)

**Co-existent infection with Chlamydia** is extremely common in patient with gonorrhoea.

**EX:** Pt with gonorrhoea and received ceftriaxone 250 mg IM single dose, but unfortunately his symptoms have not resolved. What is the most likely explanation? >> Co-existent infection with Chlamydia.

**Infertility** secondary to pelvic inflammatory disease (**PID**) is the most common complication of **gonorrhoea**. It is the second most common cause of PID after Chlamydia.

**Rectal gonococcal infection** due to unprotected **male anal homosexual** sex >>> Investigation of choice is **rectal NAAT swab** (Nucleic Acid Amplification Testing) , before ttt he should be screened for other **STDs** including HIV and the other male partner should also be screened.



### Non-gonococcal urethritis (NGU)

The incubation period is 7 to 21 days and patients often present with a **thin colourless discharge** and **absence of bacteria** on urethral swab.

The treatment for NGU is **doxycycline 100 mg twice a day for seven days** or **Azithromycin 1 g stat**. Erythromycin is second line.

**NB:** Gonococcal urethritis has a shorter incubation period of 1 to 5 days on average and causes a purulent discharge. TTT: IM ceftriaxone, azithromycin, and fluoroquinolones.

**EX:** A 23-year-old man presents with a **one week** history of dysuria and penile discharge which he describes as **thin** and **colourless**. He last had **sexual** intercourse 2 weeks prior to the onset of symptoms.

A urethral swab demonstrates 10 PMN/HPF and no bacteraemia >>> **NGU**.

### Pelvic inflammatory disease (PID)

PID is a term used to describe infection and inflammation of the female pelvic organs including the uterus, fallopian tubes, ovaries and the surrounding peritoneum. It is usually the result of ascending infection from the endocervix.

Causative organisms:

- 1) **Chlamydia trachomatis** - the most common cause
- 2) **Neisseria gonorrhoeae**: the 2<sup>nd</sup> common cause after Chlamydia.
- 3) Mycoplasma genitalium
- 4) Mycoplasma hominis

Features:

- Lower abdominal pain
- Fever
- Deep dyspareunia
- Dysuria and menstrual irregularities may occur
- Vaginal or cervical discharge
- Cervical excitation

Investigation: Screen for Chlamydia and Gonorrhoea.

Management:

- Due to the difficulty in making an accurate diagnosis, and the potential complications of untreated PID, consensus guidelines recommend **treatment once a diagnosis of PID is suspected**, rather than waiting for the results of endocervical swabs.
- **Oral ofloxacin + oral metronidazole.**
- **Or Ceftriaxone 500 mg IM STAT** followed by **oral doxycycline 100 mg BID + oral metronidazole 400 mg BD for 14 days.**
- RCOG guidelines suggest that in mild cases of PID intrauterine contraceptive devices may be left in.

Complications:

- **Infertility** - the risk may be as high as 10-20% after a single episode
- Ectopic pregnancy
- Chronic pelvic pain

### Syphilis

- Syphilis is a sexually transmitted infection caused by the **spirochaete Treponema pallidum**.
- Infection is characterised by primary, secondary and tertiary stages.
- The incubation period is between **9-90 days**.

**Primary features:** It occurs **14 days to 3 months** post exposure:

- 1) **Chancre** - **painless** ulcer at the site of sexual contact (genitalia).
- 2) **Local painless lymphadenopathy**

**EX:** A 25-year-old man presents with a single, painless, indurated ulcer on his penile shaft for the past one week. Several small, painless, inguinal lymph nodes were palpable bilaterally. His last unprotected sexual encounter was with a prostitute 3 weeks prior to presentation >>> **Chancre of 1ry Syphilis**.

**Diagnosis** of primary syphilis may be confirmed either with **dark field microscopy of secretions from the ulcer** or with **serology**.

NB: Bacterial culture of secretions from the ulcer is incorrect since *Treponema pallidum* **cannot** be **cultured** on routine bacterial culture media.

**Secondary features** - occurs **1-6 months** after primary infection:

- 1) Systemic symptoms: **fevers**, painless generalized **lymphadenopathy**
- 2) Generalized symmetrical **rash** on trunk, palms and soles
- 3) **Buccal 'snail track' ulcers** (30%)
- 4) **Condylomata lata**.

**Tertiary features (cardio-syphilis & Neuro-syphilis)**: occurs up to **10-25 years** following the original inoculation.

- 1) **Gummas**
- 2) **Cardiovascular syphilis: AA** Aortic aneurysms, Aortic regurgitation and Aortitis.
- 3) **Neurosyphilis:**
  - **GPI** (General paralysis of the insane): Gradual onset confusion, Hallucinations, Tremors, Fits, Cognitive impairment, Hyperreflexia, and Argyll-Robertson pupils.
  - **TD** Tabes dorsalis

**Features of congenital syphilis:**

- 1) **Blunted upper incisor teeth**
- 2) **Saddle nose**
- 3) **deafness**
- 4) Keratitis
- 5) Saber shins

**Investigation:**

T.P. is a very sensitive organism and cannot be grown on artificial media.

The diagnosis is therefore usually based on clinical features, serology and microscopic examination of infected tissue.

Serological tests can be divided into:

- 1) Cardiophilin tests (not treponeme specific): VDRL and RPR.
- 2) Treponemal specific antibody tests: TPHA.

**1) Cardiolipin tests:**

- Syphilis infection leads to the production of non-specific antibodies that react to Cardiolipin.
- Examples include **VDRL** (Venereal Disease Research Laboratory) & **RPR** (rapid plasma reagin)
- Insensitive in late syphilis
- Becomes negative after treatment.
- **Causes of false positive Cardiolipin tests:**
  - 1) Pregnancy
  - 2) SLE, anti-phospholipid syndrome
  - 3) TB
  - 4) HIV
  - 5) Leprosy
  - 6) Malaria

**2) Treponemal specific antibody tests:**

- Example: **TPHA** (Treponema pallidum Haem Agglutination test)
- Remains positive all the life even after treatment (التفة : وصمة العار)
- The titre of TAPHA is meaningless and should not be done.
- TPHA is positive for both syphilis and Yaws (caused by Treponema pertenue).

**Management:**

- **Benzyl-penicillin long-acting 2.4 million units single IM injection.**
- Alternatives: **doxycycline**

**The Jarisch-Herxheimer reaction** is sometimes seen following treatment.

It occurs in up to **50%** of patients with **primary** syphilis, up to **90%** of patients with **secondary** syphilis, and 25% with early latent syphilis. It is very rare in late syphilis but may be dangerous if there are lesions around important anatomical sites (for example, sinoatrial node, larynx)

It start **within 12 hours** of the 1st dose of ttt and resolving within 24 hours.

It is usually not important in early syphilis unless there is neurological or ophthalmic involvement or in pregnancy when it may cause fetal distress and premature labour.

There will be Fever, rash, hypotension, tachycardia after first dose of antibiotic. It is thought to be due to the release of **endotoxins** following bacterial death and typically occurs within a few hours of treatment.

The reaction was originally described with **syphilis** treatment but is also well described in **rickettsial** diseases such as **Lyme** disease and **Q fever**.

A single dose of benzathine penicillin should cure most cases of **early syphilis**, thus **no further antibiotics should be necessary**.

### **Q fever**

Q fever is a rickettsial zoonotic disease caused by *Coxiella burnetii*.

Q fever is usually a **self-limited respiratory illness** due to the inhalation of infected aerosols, especially from animal products.

Chronic infection may become established and can manifest as hepatitis, osteomyelitis or endocarditis.

In **Q fever endocarditis**, the **aortic valve** is involved in over 80% of cases. A murmur is not always present, but augmentation of an existing murmur may occur. Low-grade fever (or no fever), signs of heart failure, hepatosplenomegaly, clubbing, arterial emboli, and leukocytoclastic vasculitic rash may also be present.

Laboratory tests often show:

- Hepatitis
- **Anaemia**
- Elevated erythrocyte sedimentation rate
- **Thrombocytopenia** and
- Hypergammaglobulinaemia.
- Microscopic haematuria may be present.

The disease may be complicated by immune complex-mediated glomerulonephritis and arterial emboli.

The diagnosis is best made serologically and a phase I antibody titre to *Coxiella burnetii* (IgG and/or IgA) greater than 1:200 is virtually diagnostic of Q fever endocarditis.

## Yaws

It is caused by Treponema pertenue, a **non-venereal treponemal** disease which is similar to syphilis may persist for many years.

**Neurological** involvement in Yaws is currently debated.

Serological testing is indistinguishable from that seen for syphilis, and differentiation is made on history and clinical picture.

Like syphilis, **penicillin** remains the drug of choice for ttt of Yaws, with erythromycin, tetracycline or doxycycline being possible alternatives.

Patients with Yaws, particularly where the infection is chronic, may require re-treatment every few years.

## Chancroid

It is a tropical disease caused by **haemophilus ducreyi**.

It is a **Gram negative rod** which is frequent cause of genital ulceration in Rwanda.

Chancroid is endemic in parts of the Caribbean basin, Africa and South West Asia, and is commoner in non-white uncircumcised populations.

The incubation period is **approximately one week**, following which erythematous **papules** develop on the external genitalia and surrounding regions. These later develop into **pustules** and may erode into sloughy haemorrhagic **ulcers**.

It causes single or multiple **painful** genital ulcers associated with unilateral, **painful** inguinal LN enlargement.

The ulcers typically have a sharply defined, ragged, undermined border.

Gram stain of ulcer exudate: "school of fish" collection of short, thick Gm -ve rods.

Definitive diagnosis is based on **culture using enriched chocolate agar**.

TTT: Macrolides (**Azithromycin**) and **Quinolones**.

Chancr	Chancroid
<ul style="list-style-type: none"> <li>Treponema pallidum</li> <li><b>Painless</b></li> <li>Hard indurated edge</li> <li>Non exudative</li> <li>Heal spontaneously within 3-6 wks. even if no ttt</li> <li>Can be in pharynx &amp; genitalia</li> </ul>	<ul style="list-style-type: none"> <li>haemophilus ducreyi</li> <li><b>painful</b></li> <li><b>Soft</b>, ragged <b>edge</b></li> <li>Grey or yellow purulent exudate</li> </ul>

## STI: Ulcers

Genital ulcers: **(2&3)**:

- **Painful:** Herpes much more common than Chancroid.
- **Painless:** Syphilis more common than Lymphogranuloma venereum +Granuloma inguinale.

### Lymphogranuloma venereum (LGV):

It is caused by *Chlamydia trachomatis*.

There has been a recent increase in LGV among **gay men**, especially **HIV**-positive men, in London and Manchester.

Typically infection comprises of three stages:

- 1) Stage 1: small painless pustule which later forms an ulcer
- 2) Stage 2: painful inguinal lymphadenopathy
- 3) Stage 3: Proctocolitis, the inflammation can be severe causing fistula and mimicking Crohn's disease.

TTT: Azithromycin is the ttt of choice.

**Granuloma inguinale:** *Klebsiella granulomatis* (previously called *Calymmatobacterium granulomatis*)

### Other causes of genital ulcers:

- Behcet's disease
- Carcinoma

## Genital warts

Genital warts (also known as **condylomata accuminata**) are a common cause of attendance at genitourinary clinics.

They are caused by the many varieties of the human papilloma virus **HPV**, especially **types 6 & 11**.

It is now well established that HPV (primarily types **16, 18 & 33**) predisposes to **cervical cancer**.

**Features:**

- Small (2 - 5 mm) fleshy protuberances which are slightly pigmented
- May bleed or itch

**Management of genital warts:**

**1<sup>st</sup> line treatment:**

- Multiple, non-keratinised warts >> **Topical podophyllum.**
- Solitary, keratinised warts >> **Cryotherapy.**

**2<sup>nd</sup> line treatment:**

- **Imiquimod topical cream.**

Genital warts are often **resistant** to treatment and **recurrence** is common although the majority of anogenital infections with HPV clear without intervention within 1-2 years.

### Vaginal discharge

It is a common presenting symptom and is not always pathological.

Common causes:

- 1) Physiological
- 2) Bacterial vaginosis
- 3) Candida
- 4) Trichomonas vaginalis

Less common causes:

- Whilst cervical infections such as Chlamydia and Gonorrhoea can cause a vaginal discharge this is rarely the presenting symptoms.
- Ectropion.
- Foreign body.
- Cervical cancer.

Key features of the common causes are listed below:



Condition	Key features
<b>Bacterial vaginosis (BV)</b> سمك ( <i>Gardnerella vaginalis</i> )	➤ Offensive, thin, <u>white</u> /grey, <b>'fishy'</b> discharge.
<b>Candida</b> جبنة بيضاء	➤ 'Cottage cheese' discharge. ➤ Vulvitis. ➤ Itch.
<b>Trichomonas vaginalis</b> عنق الرحم فراولة وافرازات خضراء	➤ Offensive, yellow/green, frothy discharge. ➤ Vulvovaginitis. ➤ <u>Dyspareunia</u> ➤ <u>Dysuria</u> . ➤ <b>Strawberry</b> cervix.

### Bacterial vaginosis (BV)

Bacterial vaginosis (BV) describes an overgrowth of predominately **anaerobic** organisms such as **Gardnerella vaginalis**.

This leads to a consequent fall in lactic acid producing aerobic lactobacilli resulting in a ↑ vaginal pH.

Douching, washing with scented soaps and gels (Dettol) have been implicated and the patient should be advised to stop these practices.

BV is the **commonest cause of abnormal vaginal discharge** in women of **childbearing** age. It is twice as common as vaginal candidiasis.

Whilst BV is not a sexually transmitted infection it is seen almost exclusively in sexually active women.

Bacterial vaginosis - overgrowth of predominately Gardnerella vaginalis

#### **Features:**

- Vaginal discharge: **'fishy'**, offensive thin, milky white discharge which is not itchy.
- **Asymptomatic in 50%**

**Amsel's criteria for diagnosis of BV:** 3 of the following 4 points should be present:

- 1) Thin, white homogenous discharge.
- 2) Clue cells on microscopy.
- 3) ↑ Vaginal pH > 4.5
- 4) Positive whiff test (addition of potassium hydroxide results in fishy odour)

**Management:**

- **Oral metronidazole:** 500 mg twice daily given for 7 days, or alternatively, a single dose of oral metronidazole 2 g may be given.
- 70-80% initial cure rate.
- Relapse rate > 50% within 3 months.
- The BNF suggests **topical metronidazole** or **topical clindamycin** as alternatives.

**Bacterial vaginosis in pregnancy:**

- Results in an increased risk of preterm labour, low birth weight and chorioamnionitis, late miscarriage.
- It was previously taught that oral metronidazole should be avoided in the first trimester and topical clindamycin used instead.
- Recent guidelines however recommend that **oral metronidazole is used throughout pregnancy**. The BNF still advises against the use of high dose metronidazole regimes.

**Trichomonas vaginalis**

It is an **anaerobic protozoan** which thrives in more **alkaline** conditions.

The **pH of the discharge is greater than 6.5**.

T. vaginalis does not have a cyst form and therefore is transmitted directly, for example, through sexual transmission.

It causes inflammation of the vaginal endometrium and therefore makes it more susceptible to other sexually transmitted infections.

Treatment of T. vaginalis is with **metronidazole 2 g stat**.

**Sexual partners should also be treated**, as they may be **asymptomatic carriers**.

Metronidazole is relatively contraindicated in the first trimester of pregnancy and so treatment should be delayed until the second trimester.

Urinary tract infection (UTI) in adults: management

**1) Lower urinary tract infections in non-pregnant women:**

- Local antibiotic guidelines should be followed if available.
- 2012 SIGN guidelines recommend trimethoprim or nitrofurantoin for 3 days.

**2) Pregnant women with symptomatic bacteriuria** should be treated with an antibiotic for 7 days. A urine culture should be sent.

**3) For asymptomatic pregnant women:**

- A urine culture should be performed routinely at the first antenatal visit.
- If positive, a second urine culture should be sent to confirm the presence of bacteriuria.
- SIGN recommend **to treat asymptomatic bacteriuria** detected during **pregnancy** with an **antibiotic**.
- A 7 day course of antibiotics should be given.
- A further urine culture should be sent following completion of treatment as a test of cure.

So, Pregnant women with symptomatic or asymptomatic UTI >>> ttt: **R/Amoxycillin for 7 days. (500 mg x 3 x 7).**

**4) For patients with sign of acute pyelonephritis:**

- Hospital admission should be considered.
- Local antibiotic guidelines should be followed if available.
- The BNF currently recommends a broad-spectrum cephalosporin or a quinolone for 10-14 days.

**Ciprofloxacin** has still been recommended as **first** line therapy by SIGN for symptoms of **upper** UTI.

**Trimethoprim** resistance is apparently as high as 40% but it is still recommended as a 3 day course for uncomplicated **lower** UTI.

**Malaria: Falciparum**

**Clinical Feature of severe malaria:**

- 1) Prostration: generalized weakness so that the patient is unable to walk or sit up without assistance.
- 2) Temperature > 39 °C
- 3) Impaired consciousness
- 4) Multiple convulsions > 2 episodes in 24 hours.
- 5) Respiratory distress: acidotic breathing
- 6) Circulatory collapse or shock: SBP < 70 mmHg.
- 7) Jaundice
- 8) Haemoglobinuria
- 9) Abnormal spontaneous bleeding
- 10) Pulmonary oedema (CXR)

**Laboratory finding of severe malaria:**

- 1) Schizonts on a blood film
- 2) Parasitaemia > 2%
- 3) Severe anaemia: Hb < 5 gm/dl
- 4) More than 1% of RBC infected.
- 5) Hypoglycaemia: < 2.2 mmol/L or < 40 mg/dl.
- 6) Metabolic acidosis: HCO<sub>3</sub> < 15 mmol/L
- 7) Hyperlactataemia: Lactate > 5 mmol/L.
- 8) Renal impairment: Creatinine > 265 Mmol/L
- 9) Complications as below

**Complications:**

- 1) Cerebral malaria (it has a mortality of 20%): seizures, coma, hypertonia, hyperreflexia, upgoing planters, nystagmus and papilledema.
- 2) ARF: black water fever, 2ry to intravascular hemolysis, mechanism unknown.
- 3) ARDS >> ↑Respiratory rate
- 4) DIC >> ↓Platelets
- 5) Hypoglycaemia

**Uncomplicated falciparum malaria:**

- Strains resistant to chloroquine are prevalent in certain areas of Asia and Africa.
- The 2010 WHO guidelines recommend artemisinin-based combination therapies (ACTs) as first-line therapy
- Examples include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine.
- Both artemether and atovaquone are not currently recommended in pregnancy.

**Severe falciparum malaria:**

- A parasite counts of more than 2% will usually need parenteral treatment irrespective of clinical state.
- **IV Artesunate** is now recommended by **WHO** in preference to intravenous quinine.
- If parasite count > 10% then exchange transfusion should be considered.
- Shock may indicate coexistent bacterial septicaemia - malaria rarely causes haemodynamic collapse.

**Severe falciparum malaria >>> TTT: IV Artesunate or IV Quinine**

**Important notes:**

If one thick and thin film is negative, it should be repeated if the diagnosis is strongly suspected as **3 or more films are usually required to exclude malaria**.

**Hypoglycaemia** is an important side effect of **quinine** therapy and should be monitored in those having IV quinine.

**IV quinine** is reserved for **severe** or **cerebral malaria** (most deaths from M. falciparum occur in first 96 hours of starting treatment).

The initial dose should **NOT** be reduced in those patients severely ill with **renal** or **hepatic** impairment.

**Pregnancy is NOT a contraindication for quinine**

**WHO Guidelines (2006)** recommend:

-In the **first** trimester, both **Artesunate** and **quinine**.

-In the second and third trimester, **Artemisinin**s are first line.

In severe malaria in pregnancy, any available treatment should be started without delay as both the mother and foetus' life are in danger.

It is as yet unclear exactly the role that the spleen plays in malaria parasites clearance, but case series suggest that **splenectomy** may be associated with **reduced** parasite **clearance** despite optimal anti-malarial therapy.

**EX:** Pt 30 yrs old has previous splenectomy dt RTA, and then after Asia trip he has hypotension, fever, low PLT, haemolysis >>> **Falciparum malaria**.

**EX:** 19 year old male from Zambia has **severe falciparum malaria**, renal impairment, **renal failure**, **massive haemolysis**, **black urine**, **anuria (Blackwater fever)** >>> TTT: **IV Quinine** loading dose 20 mg/kg (up to maximum dose 1.4 gm) infused over 4 hours ± haemodialysis..

### **Malaria: non-falciparum**

The most common cause of non-falciparum malaria is ***Plasmodium vivax***, with *Plasmodium ovale* and *Plasmodium malariae* accounting for the other cases.

*Plasmodium vivax* is often found in Central America and the Indian Subcontinent whilst *Plasmodium ovale* typically comes from Africa.

Features:

- General features of malaria: fever, headache, splenomegaly.
- *Plasmodium vivax/ovale*: **cyclical fever every 48 hours**.
- *Plasmodium malariae*: **cyclical fever every 72 hours**.
- *Plasmodium malariae*: is associated with nephrotic syndrome.

Treatment:

- Non-falciparum malarias are almost always **chloroquine sensitive**.
- Patients with ovale or vivax malaria should be given **primaquine following acute treatment with chloroquine** to destroy liver hypnozoites and prevent relapse.

**N.B:** Vivax and Ovale malaria have a hypnozoite stage and may therefore relapse following treatment.

**NB:** The **Duffy antigen** receptor on RBCs facilitates the entry of **P. vivax** into the **RBCs** and Duffy negative individuals are therefore resistant to this strain.

A similar situation exists with *P. ovale* but Duffy negative offers slightly less protection.

### Malaria: prophylaxis

There are around 1,500-2,000 cases each year of malaria in patients returning from endemic countries.

The majority of these cases (around 75%) are caused by the potentially fatal *Plasmodium falciparum* protozoa.

The majority of patients who develop malaria did not take prophylaxis.

**Prophylaxis does not give full protection.**

**Atovaquone + Proguanil combination** is given **1-2 days before** the travel and should be continued **7 days after return**.

It should also be remembered that UK citizens who originate from malaria endemic areas quickly lose their innate immunity.

Drug	Side-effects + notes	Time to begin before travel	Time to end after travel
<b>Atovaquone + Proguanil</b> (Malarone)	GI upset	<b>1 - 2 days</b>	<b>7 days</b>
Chloroquine	<ul style="list-style-type: none"> <li>➤ Headache</li> <li>➤ Contraindicated in epilepsy</li> <li>➤ Taken weekly</li> </ul>	1 week	4 weeks
Doxycycline	<ul style="list-style-type: none"> <li>➤ Photosensitivity</li> <li>➤ Oesophagitis</li> </ul>	1 - 2 days	4 weeks
Mefloquine (Lariam)	<ul style="list-style-type: none"> <li>➤ Dizziness</li> <li>➤ Neuropsychiatric disturbance</li> <li>➤ Contraindicated in epilepsy</li> <li>➤ Taken weekly</li> </ul>	2 - 3 weeks	4 weeks
Proguanil (Paludrine)		1 week	4 weeks
Proguanil + chloroquine	See above	1 week	4 weeks

In certain parts of South-East Asia there is widespread chloroquine resistance. Chemoprophylaxis using atovaquone + proguanil (Malarone), mefloquine (Lariam) or doxycycline is therefore recommended.

**Pregnant women** should be advised to avoid travelling to regions where malaria is endemic. Diagnosis can also be difficult as parasites may not be detectable in the blood film due to placental sequestration. However, if travel cannot be avoided:

- **Chloroquine** can be taken
- Proguanil: folate supplementation (5mg od) should be given
- Malarone (atovaquone + proguanil): the BNF advises to avoid these drugs unless essential. If taken then folate supplementation should be given
- Mefloquine: caution advised
- Doxycycline is contraindicated

It is again advisable to avoid travel to malaria endemic regions with **children** if avoidable. However, if travel is essential then children should take malarial prophylaxis as they are more at risk of serious complications.

- Diethyltoluamide (**DEET**) 20-50% can be used in children over 2 months of age.
- **Doxycycline** is only licensed in the UK for children **over** the age of 12 years.

- **Doxycycline** prophylaxis is the **safest** option with less resistance in many parts of the world compared to the other options available.
- Chloroquine prophylaxis has high levels of resistance to the drug around the world.
- Mefloquine prophylaxis is contradicted if the patient has a mental illness.



### **Schistosomiasis**

Schistosomiasis, or bilharzia, is a parasitic flatworm infection. The following types of schistosomiasis are recognised:

- *Schistosoma haematobium*: urinary schistosomiasis.
- *Schistosoma mansoni* and *Schistosoma intercalatum*: intestinal schistosomiasis.
- *Schistosoma japonicum* is prevalent in China, Indonesia, Thailand and the Philippines mainly. It is the commonest cause of Schistosoma encephalitis. Its eggs are smaller unlike those of *S. mansoni* and *S. haematobium* which are more likely to cause spinal cord schistosomiasis because of their larger size and spikes which do not enable them get to the brain hence the infection in the spinal cord.

#### **Schistosoma haematobium:**

This typically presents as a '**swimmer's itch**' in patients who have recently returned from **Africa**.

Also occur in Middle East, Portugal, Spain and Greece.

Schistosoma haematobium is a risk factor for **squamous cell bladder cancer**.

#### **Features:**

- Frequency
- Haematuria
- Haemospermia (occasionally)
- **Bladder calcification**
- It may progress to hydronephrosis and renal failure.

#### **Management:**

- Single oral dose of praziquantel.
- Praziquantel is not licensed for human use in the UK but is available on named patient basis.
- For *S. haematobium* and *S. mansoni*: **Praziquantel 40 mg/kg per day for 3 days** is recommended.
- For *S. japonicum*: **Praziquantel 60 mg/kg per day for 6 days** with a maximum dose of 5 grams per day **with prednisolone 1 mg/kg/day**.

**NB:** Since some of the pathology in **neuro-schistosomiasis** is secondary to **hypersensitivity** reactions there is need to use a **steroid**, in this case **prednisolone 1 mg/kg per day**. There is no consensus about when it should be started or stopped.

**N.B:**

- *Schistosoma haematobium* causes **haematuria**.
- Schistosomiasis is the most common cause of **bladder calcification** worldwide.
- Schistosomiasis is a risk factor for Squamous cell bladder cancer. (NOT Transitional cell carcinoma).

### Leishmaniasis

Leishmaniasis is caused by the intracellular protozoa *Leishmania*, usually being spread by sand flies.

The organism multiply in monocytes and macrophages, its incubation period may extend up to 10 years.

3 forms are seen: Cutaneous, mucocutaneous and visceral.

**Cutaneous leishmaniasis:**

- Caused by *Leishmania tropica* or *Leishmania mexicana*
- Crusted lesion at site of bite
- May be underlying ulcer

**Mucocutaneous leishmaniasis:**

- Caused by ***Leishmania brasiliensis***
- Skin lesions may spread to involve mucosae of nose, pharynx etc.

**Visceral leishmaniasis (Kala-azar):**

- Mostly caused by ***Leishmania donovani***.
- Occurs **Mediterranean**, Asia, South America, and Africa.
- The most common cause in **Southern Europe e.g. Turkey** is ***Leishmania Infantum***.
- Fever, night sweats, rigors
- Generalized lymphadenopathy.
- Massive splenomegaly.

- Hepatomegaly
- Pancytopenia secondary to hypersplenism
- Poor appetite, weight loss.
- Occasionally patients may report increased appetite with paradoxical weight loss.
- Grey skin - 'kala-azar' it is an indian name which means darkening of the skin; black sickness or black fever.
- Leishmaniasis can be cultured from spleen, bone marrow and liver.
- TTT: Na stibogluconate is the mainstay of therapy, Amphotericin B is a possible alternative.

EX: Turkish male with fever, exhaustion, rash, dark skin, HSM and generalized lymphadenopathy >>> **Leishmania Infantum**.

Mucocutaneous ulceration following travel? >>> *Leishmania brasiliensis*

### Toxoplasmosis

**Toxoplasma gondii** is a **protozoa** which infects the body via the GI tract, lung or broken skin.

Its oocysts release trophozoites which migrate widely around the body including to the eye, brain and muscle.

The usual animal reservoir is the cat, although others such as rats carry the disease.

**Most** infections are **asymptomatic**.

Symptomatic patients usually have a **self-limiting infection**, often having clinical features resembling infectious mononucleosis (fever, malaise, and lymphadenopathy). Other less common manifestations include meningoencephalitis and myocarditis.

Investigation:

- Antibody test
- Sabin-Feldman dye test

Treatment is usually reserved for those with severe infections or patients who are immunosuppressed.

- **Pyrimethamine + sulphadiazine for at least 6 weeks.**

Congenital toxoplasmosis is due to transplacental spread from the mother. It causes a variety of effects to the unborn child including microcephaly, hydrocephalus, cerebral calcification and choroidoretinitis.

### Trypanosomiasis

-Two main form of this protozoal disease are recognised - African Trypanosomiasis (sleeping sickness) and American Trypanosomiasis (Chagas' disease)

-Two forms of **African trypanosomiasis**, or **sleeping sickness**, are seen - *Trypanosoma gambiense* in West Africa and *Trypanosoma rhodesiense* in East Africa. Both types are spread by the tsetse fly.

-*Trypanosoma rhodesiense* tends to follow a more acute course. Clinical features:

- 1) Trypanosoma chancre - painless SC nodule at site of infection.
- 2) Intermittent fever.
- 3) Enlargement of posterior cervical lymph nodes.
- 4) Later: CNS involvement e.g. somnolence, headaches, mood changes, meningoencephalitis.

-Management:

- Early disease: IV pentamidine or Suramin.
- Later disease or central nervous system involvement: IV Melarsoprol.

-**American trypanosomiasis**, or **Chagas' disease**, is caused by the protozoan *Trypanosoma cruzi*. The vast majority of patients (95%) are asymptomatic in the acute phase although a chagoma (an erythematous nodule at site of infection) and periorbital oedema are sometimes seen. Chronic Chagas' disease mainly affects the heart and gastrointestinal tract.

- **Heart: Myocarditis** may lead to heart failure, RBBB, arrhythmias and increased risk of thromboembolism (DVT/PE).
- **GIT** features: includes megaoesophagus and megacolon causing **dysphagia** and constipation.

**Cardiac involvement is the leading cause of death in Pt with Chagas' disease.**

Management:

- Treatment is most effective in the **acute** phase using azole or nitroderivatives such as Benznidazole or Nifurtimox.
- Chronic disease management involves treating the complications e.g., heart failure.

### **Tape worms**

Tape worms are made up of repeated segments called proglottids.

These are often present in faeces and are useful diagnostically.

#### **Hydatid disease:**

- Caused by the Echinococcus granulosus (dog tapeworm).
- Life-cycle involves dogs ingesting hydatid cysts from sheep liver.
- The adult worm is found normally in the dog and sheep intestine and man is an accidental intermediate host.
- The infection is seen in Mediterranean areas, East Africa, Australia and South America.
- Often seen in farmers.
- The liver is the commonest organ involved and may cause liver cysts >> pressure effect with obstructive jaundice.
- Minor leaks lead to increased pain and a mild allergic reaction characterised by flushing and urticaria.
- Major rupture can lead to a full-blown anaphylactic reaction in some cases.
- **CT abdomen** has an accuracy of 98% and the sensitivity to demonstrate the daughter cysts, it is the best test for the differentiation of hydatid from amoebic and pyogenic cysts in the liver.
- TTT: Albendazole and aspiration.

#### **Cysticercosis:**

- Caused by Taenia saginata (from beef) and Taenia solium (from pork).
- It can affect either the intestine, causing an intestinal tapeworm infection, or the CNS, causing **neurocysticercosis** (seizures, CT brain shows periventricular cystic lesion in the parietal lobe with surrounding oedema).
- For confirming the diagnosis of neurocysticercosis:
  - Serum anticysticercal antibodies demonstrated by immunoblot assay.
  - CSF-ELISA for detection of cysticercal antigens.
  - Resolution of intracranial cystic lesions after albendazole therapy.
  - Fundus examination for direct visualization of subretinal parasites.
- TTT: Niclosamide.

## Nematodes

### Ancylostoma braziliense:

- **Most common** cause of **cutaneous larva migrans**
- Common in Central and Southern America
- TTT: **Thiabendazole**.

### Strongyloides stercoralis:

- Acquired percutaneously (e.g. walking barefoot).
- Causes pruritus and larva currens - this has a similar appearance to cutaneous larva migrans but moves through the skin at a far greater rate.
- Abdominal pain, diarrhoea, pneumonitis.
- Papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks.
- Larva currens: pruritic, **linear erythematous rash over groins and buttocks**.
- If the larvae migrate to the **lungs** a pneumonitis similar to Loeffler's syndrome may be triggered.
- May cause Gram negative septicaemia due carrying of bacteria into bloodstream.
- Eosinophilia sometimes seen.
- Management: **Ivermectin** and albendazole also used as an alternative, particularly in chronic infections.

If patient has chronic diarrhoea and has **both positive HIV and positive serology for strongyloides** >>> you should treat the **strongyloides** infection **firstly** with **ivermectin** a short time before commencing **HAART** for the HIV.

### Toxocara canis:

- Commonly acquired by ingesting eggs from soil contaminated by dog faeces.
- **Commonest cause of visceral larva migrans.**
- Other features: eye granulomas, liver/lung involvement.

### **Scabies**

Scabies is caused by the mite *Sarcoptes scabiei* and is spread by prolonged skin contact. It typically affects children and young adults.

Scabies should be suspected in any sexually active young person who presents with generalised pruritus without any specific signs.

The scabies mite burrows into the skin, laying its eggs in the stratum corneum.

The intense pruritus associated with scabies is due to a **delayed type IV hypersensitivity reaction** to mites/eggs which occurs about 30 days after the initial infection.

Features:

- Widespread pruritus.
- **Linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist.**
- In infants the face and scalp may also be affected.
- Secondary features are seen due to scratching: excoriation, infection.

Diagnosis: by demonstrating *Sarcoptes scabiei* on **skin scrapings**.

Management:

- **Permethrin** 5% is first-line
- **Malathion** 0.5% is second-line
- Give appropriate guidance on use (see below)
- **Pruritus persists for up to 4-6 weeks post eradication.** (i.e. It is normal for pruritus to persist for up to 4-6 weeks post eradication and it needs no further ttt)

Patient guidance on treatment (from Clinical Knowledge Summaries):

- Avoid close physical contact with others until treatment is complete.
- **All household and close physical contacts should be treated at the same time, even if asymptomatic.** علاج لكل البيت حتى لو مفيش أعراض
- Launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

The BNF advises to apply the insecticide to **all areas**, including the face and scalp, contrary to the manufacturer's recommendation. Patients should be given the following instructions:

- Apply the insecticide cream or liquid to cool, dry skin.
- Pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow.
- **Allow to dry and leave on the skin for 8-12 hours for Permethrin, or for 24 hours for Malathion, before washing off.**
- Reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc.
- **Repeat treatment 7 days later.**

### **Crusted (Norwegian) scabies:**

- Crusted scabies is seen in patients with suppressed immunity, especially HIV.
- The crusted skin will be teeming with hundreds of thousands of organisms.
- Ivermectin is the treatment of choice and isolation is essential.

### **Animal bites**

The majority of bites seen in everyday practice involve **dogs** and **cats**.

These are generally polymicrobial but the most common isolated organism is Pasteurella multocida.

Management:

- Cleanse wound
- Current BNF recommendation is **co-amoxiclav**.
- If penicillin-allergic then **doxycycline + metronidazole** is recommended.

### **Cat scratch disease**

It is generally caused by the Gram negative rod **Bartonella henselae**.

Features:

- Fever
- History of a cat scratch
- Regional lymphadenopathy
- Headache, malaise



## Rabies

- Rabies is a viral disease that causes an acute progressive encephalitis.
- The rabies virus is classed as a RNA rhabdovirus and has a bullet shaped capsid.
- Incubation period is 1 – 3 months.
- It is commonly transmitted by bat, raccoon and skunk bites. Following a bite the virus travels up the nerve axons towards the CNS in a retrograde fashion.
- **Once symptoms begin, treatment is largely useless.**
- Patients usually die within days to weeks after presentation.

Features:

- 1) Prodrome: headache, fever, agitation.
- 2) Hydrophobia: water-provoking muscle spasms.
- 3) Hypersalivation.
- 4) Negri bodies: cytoplasmic inclusion bodies found in infected neurons.

There is now considered to be '**no risk**' of developing rabies following an animal bite in the UK and the majority of developed countries.

If the suspicion of rabies is low, i.e. the dog seemed healthy, only minor abrasions through double layers cloths, abrasions were washed well; so prophylaxis is not indicated.

Instead, **the animal (dog) should be confined and observed daily for 10 days** by a vet and **if it exhibits signs of rabies** during the 10-day observation period, the patient should immediately receive **prophylaxis** and the animal should be **killed** and its **brain tissue tested for rabies**.

If the bite occurred in an area where rabies is endemic, immediate post exposure prophylaxis is warranted, either with locally produced biologic agents or those obtained from the closest major urban area or country.

Following an animal bite in at risk countries:

- If an individual is already immunised then 2 further doses of vaccine should be given.
- If not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination.

Rabies - following possible exposure >>>

Give **human rabies immunoglobulin (HRIG) + full course of vaccination**.

### Pyogenic liver abscess

Management:

- **Drainage** (needle aspiration or catheter) should always be performed.
- **Amoxicillin + ciprofloxacin + metronidazole.**
- If penicillin allergic: ciprofloxacin + clindamycin.

### Tetanus

- Tetanus is caused by the tetanospasmin exotoxin released from *Clostridium tetani*.
- Tetanus spores are present in soil and may be introduced into the body from a wound, which is often unnoticed.
- Tetanospasmin prevents release of GABA.

Features:

- Prodrome fever, lethargy, headache
- **Trismus (lockjaw or jaw spasm)**
- **Risus sardonicus**
- **Opisthotonus** (arched back, hyperextended neck)
- Spasms (e.g. **dysphagia**)
- **Cephalic tetanus** means involving the cranial nerves usually from a wound on the head and neck. It causes severe dysphagia. It may be confused with rabies but hydrophobia never occurs.

Management:

- 1) **Supportive** ttt: including **ventilatory** support and **muscle relaxants**.
- 2) **I.M human tetanus immunoglobulin** for high-risk wounds (e.g. compound fractures, delayed surgical intervention, significant degree of devitalised tissue).
- 3) **I.V Metronidazole** is now preferred to **benzylpenicillin** as the antibiotic of choice.

**NB:** While *Clostridium*-specific intravenous immunoglobulin **IVIG** is **ineffective** once the toxin is attached to **nervous** tissue **it may prevent progression**.

**NB:** Absence of a wound does not exclude tetanus.

**Tetanus: vaccination**

The tetanus vaccine is a cell-free purified toxin that is normally given as part of a combined vaccine.

Tetanus vaccine is currently given in the UK as part of the routine immunisation schedule at:

- 1) 2 months
- 2) 3 months
- 3) 4 months
- 4) 3-5 years
- 5) 13-18 years

This therefore provides 5 doses of tetanus-containing vaccine.

Five doses is now considered to provide adequate long-term protection against tetanus.

**I.M human tetanus immunoglobulin** should be given to patients with high-risk wounds (e.g. Compound fractures, delayed surgical intervention, significant degree of devitalised tissue) irrespective of whether 5 doses of tetanus vaccine have previously been given.

If vaccination history is incomplete or unknown then **a dose of tetanus vaccine** should be given combined with intramuscular human tetanus immunoglobulin for high-risk wounds.

TTT to prevent the development of tetanus:

Clean wound + **I.M human tetanus immunoglobulin** ± **Tetanus vaccine** ± **Antibiotic (Metronidazole IV)**.

**Gas gangrene**

It is caused by **Clostridium perfringens** (or other Clostridium spp).

Infection often follows trauma and contamination of the wound by soil containing clostridial spores.

Patients with gas gangrene tend to be more systemically unwell than the degree of cellulitis would suggest and urgent surgical attention may prevent death.

TTT: **Urgent surgical debridement**, high dose **benzyl-penicillin** and **clindamycin**, and **hyperbaric oxygen** if available.

**Orf**

Orf is generally a condition found in sheep and goats although it can be transmitted to humans. It is caused by the **parapox virus**.

**In animals:** 'Scabby' lesions around the mouth and nose.

**In humans:**

- Generally affects the hands and arms of the **farmer**.
- **Initially** small, raised, red-blue papules.
- **Later** may increase in size to 2-3 cm and become flat-topped and haemorrhagic.

**Salmonella (Typhoid fever) (Enteric fever)**

- The Salmonella group contains many members, most of which cause diarrhoeal diseases.
- They are **aerobic, Gram negative rods** which are **not normally** present as commensals in the gut.
- Typhoid and paratyphoid are caused by Salmonella typhi and Salmonella paratyphi (types A, B & C) respectively.
- They are often termed enteric fevers, producing systemic symptoms such as headache, fever, myalgia and arthralgia.
- Typhoid fever is seen in travellers returning from countries in the developing world e.g. India.
- Salmonella typhi has an **incubation period 1-3 weeks** followed by a prodrome of flu-like symptoms.
- It is often difficult to differentiate typhoid from malaria clinically.
- **Blood culture** is the **diagnostic** method of choice: **Gm –ve bacilli** of S. typhi.
- **Faecal culture** is positive in **only 50%** of cases during the **first week** of illness.
- **Serology by Widal test is not performed routinely in UK.**
- Vaccinated individuals who develop the disease will have a **higher** threshold but the same disease.

Features:

- Initially systemic upset as above.
- **Fever with Relative bradycardia.**
- Abdominal pain, distension and possible hepatosplenomegaly.
- **Constipation:** although Salmonella is a recognised cause of diarrhoea, constipation is more common in typhoid.

- **Salmon-coloured rose spots:** present on the **trunk** in **40%** of patients, they are faint, maculopapular blanching lesions and are more common in paratyphoid.

Possible complications include:

- Osteomyelitis (especially in sickle cell disease where Salmonella is one of the most common pathogens).
- GI bleed/perforation.
- Meningitis
- **Cholecystitis:** The gallbladder may act as a **reservoir** of infection and cause relapse in individuals treated with antibiotics. Cholecystectomy may be indicated.
- **Chronic carriage** (1%, more likely if adult **females**): Children are rarely chronic carriers of the organism although for some unknown reason females are more commonly long term carriers than males (remember: Typhoid Mary).

The disease has stages as follow:

<b>Week 1</b>	Pyrexia and relative bradycardia
<b>Week 2</b>	<ul style="list-style-type: none"> <li>-Maculopapular salmon-coloured rash that blanches on pressure.</li> <li>-Hepatosplenomegaly.</li> <li>-Lymphadenopathy.</li> </ul>
<b>Week 3</b>	<p>Complications:</p> <ul style="list-style-type: none"> <li>-Lobar pneumonia</li> <li>-Endocarditis</li> <li>-Haemolytic anaemia</li> <li>GIT bleeding/perforation</li> <li>-Meningitis</li> <li>-Acute cholecystitis</li> <li>-Osteomyelitis</li> </ul>

TTT:

- 1) **Azithromycin** is usually preferred as the **oral** option for stable patient.
- 2) **Ceftriaxone IV** for more **severe** disease.
- 3) There is extensive quinolones resistance (reach to 80% in some areas).
- 4) If the patient works in hospitality industry he should provide a negative specimen prior to returning to work.

### Shigella

Overview:

- Causes bloody diarrhoea, abdominal pain.
- Severity depends on type: S sonnei (e.g. from UK) may be mild, S flexneri or S dysenteriae from abroad may cause severe disease.
- TTT: **Ciprofloxacin**

### Escherichia coli

Escherichia coli is a **facultative anaerobic**, lactose-fermenting, Gram negative rod which is a normal gut commensal.

E. coli infections lead to a variety of diseases in humans including:

- 1) Diarrhoeal illnesses.
- 2) UTIs.
- 3) Neonatal meningitis.

### E-coli Serotypes:

It is classified according to the antigens which may trigger an immune response:

Antigen	Origin	Notes
O	Lipopolysaccharide layer	
K	Capsule	Neonatal meningitis secondary to E. coli is usually caused by a serotype that contains the capsular antigen K-1
H	Flagellin	

**E. coli O157:H7** is a particular strain associated with severe, haemorrhagic, watery diarrhoea. It has a high mortality rate and can be complicated by **haemolytic uraemic syndrome (HUS)**. It is often spread by contaminated ground beef. The presentation is usually: **Diarrhea+ Renal imp+ ↓Hb+ ↓PLT**.

### Giardiasis

Giardiasis is caused by the flagellate protozoan **Giardia lamblia**. It is spread by the faeco-oral route.

Features:

- **Often asymptomatic**
- Lethargy, bloating, abdominal pain
- Non-bloody diarrhoea
- Chronic diarrhoea, malabsorption and lactose intolerance can occur
- Stool microscopy for trophozoite and cysts are classically negative, therefore duodenal fluid aspirates or 'string tests' (fluid absorbed onto swallowed string) are sometimes needed.

TTT: **Metronidazole**.

### Cholera

It is caused by *Vibrio cholerae* - Gram negative bacteria.

Features:

- **Profuse 'rice water' diarrhoea**
- Dehydration
- Hypoglycaemia

Management:

- Oral rehydration therapy
- Antibiotics: **doxycycline**, **ciprofloxacin**.

"Individuals with blood group **O** are more susceptible than other individuals to severe cholera, although the mechanism is unknown."

**Pyrexia of unknown origin (PUO)**

Prolonged fever of > 3 weeks which resists diagnosis after a week in hospital.

**1) Neoplasia:**

- Preleukaemia
- Lymphoma
- Hypernephroma
- Atrial myxoma

**2) Infections:**

- Abscess
- TB

**3) Connective tissue disorders:**

**Lymphadenopathy (causes of generalised lymphadenopathy):**

**Infective:**

- EBV (Infectious mononucleosis)
- HIV, including seroconversion illness
- Eczema with secondary infection
- Toxoplasmosis
- Rubella
- CMV
- T.B
- Roseola infantum

**Neoplastic:** Leukaemia & Lymphoma

**Others**

- Autoimmune conditions: SLE, rheumatoid arthritis
- Sarcoidosis
- GVHS
- Drugs: phenytoin and to a lesser extent allopurinol, isoniazid

**N.B:** Kawasaki disease causes only cervical lymphadenopathy



### African Tick Typhus

It is caused by Rickettsiae

Features:

- Hx of tick bites
- **Black spots** on forearm/thigh
- Low grade fever
- Faint maculopapular rash

TTT: **Doxycycline 100 mg single dose** leads to rapid clinical recovery.

### Rocky Mountain spotted fever (RMSF)

It is the most lethal and most frequently reported rickettsial infection, spread by **ticks**, common in **USA**.

It is caused by **Rickettsia rickettsii**.

Physicians must maintain a high index of suspicion for RMSF in patients who are febrile as it is essentially a clinical diagnosis.

Patients with **unexplained febrile illness**, even if they have no history of a tick bite or travel to an endemic area but have **palms & soles rash and myalgia** should be suspected to RMSF.

**Rash is a major diagnostic sign**, the maculopapular rash usually appears **2-6 days after onset of fever** and progresses through stages and distributions that are never pathognomonic, the rash begins on the wrists (**palms**) and ankles (**soles**) and spreads centripetally to involve the trunk and extremities, later the rash becomes petechial in 50% of patients.

Features:

- 1) Fever
- 2) Rash on hands, feet which later >>> desquamate (peel)
- 3) Tachycardia with **NO HYPOTENSION** (unlike Staph Toxic Shock Syndrome)
- 4) Sometimes, leukopenia and thrombocytopenia.

TTT: **Doxycycline**.

### Mediterranean Spotted Fever (Boutonneuse fever)

It is a fever caused by the Rickettsia conorii and transmitted by the dog tick Rhipicephalus sanguineus.

Features:

- Incubation period: 7 days
- It manifests abruptly with **high fevers, chills, myalgia**, joint pain **severe headache**, photophobia and diarrhea.

- The location of the bite forms a **black spots or ulcerous crust** (tache noire).
- Around the 4<sup>th</sup> day of the illness an **exanthema (widespread rash)** appears, first macular then maculopapular and sometimes petechial.

TTT: Doxycycline.

### **Dengue fever**

Dengue fever is a viral infection which can progress to **viral haemorrhagic fever** (also yellow fever, Lassa fever, Ebola).

Basics:

- Transmitted (carried) by the **Aedes aegypti mosquito** in endemic areas as South East Asia (Indonesia) and North Australia.
- There are 4 serotypes.
- Incubation period of 7 days.
- The patient often experiences a sudden onset of fever, headache, and retro-orbital pain and back pains with severe myalgia hence the name break bone fever.
- A form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop: clotting abnormalities and a bleeding diathesis.
- Around 20-30% of these patients go on to develop dengue shock syndrome (DSS).

Features:

- 1) Severe fever up to 40.
- 2) Severe headache (often retro-orbital & frontal)
- 3) Generalized maculopapular rash: palatal vesicles and sclera injection
- 4) Facial flushing (dengue)
- 5) Myalgia
- 6) Pleuritic pain
- 7) Low TLC & Low platelet count in 50% of patients.
- 8) Raised transaminase level (ALT).
- 9) Low Na.

**TTT:**

- Treatment is entirely **supportive** (symptomatic) e.g. **fluid resuscitation (Normal Saline)** and **pain relief**.
- But other patients who develop thrombocytopenia and bleeding diathesis may require blood transfusion, and correction of clotting etc.
- (Corticosteroids have NO role).

**Babesiosis**

It is a **tick-borne malaria-like illness** caused by species of the intraerythrocytic protozoan **Babesia**.

Babesiosis is a **clinical diagnosis**.

Patients present with similar symptoms to malaria i.e. fever, chills and rigors.

The intraerythrocytic Babesia destroy the RBCs causing **hemolytic anaemia** and **haemoglobinuria** with secondary reactive **polyclonal hypergammaglobulinaemia**.

Symptoms are greater with a higher percentage of parasitism.

Babesiosis is frequent in endemic areas of the **USA**, particularly Long Island, New York, Nantucket Martha's Vineyard and Massachusetts.

Patients without a spleen have a more fulminant and prolonged clinical course and may have overwhelming infection and a fatal outcome.

**Congenital infections** (e.g. rubella, toxoplasmosis and cytomegalovirus).

**Cytomegalovirus is the most common congenital infection in the UK.** Maternal infection is usually asymptomatic.

	<b>Rubella</b>	<b>Toxoplasmosis</b>	<b>CMV</b>
<b>Characteristic features</b>	<ul style="list-style-type: none"> <li>➤ <b>Sensorineural deafness.</b></li> <li>➤ <b>Congenital cataracts.</b></li> <li>➤ Glaucoma.</li> <li>➤ Congenital heart disease (e.g. PDA).</li> </ul>	<ul style="list-style-type: none"> <li>➤ <b>Cerebral calcification.</b></li> <li>➤ <b>Chorioretinitis.</b></li> <li>➤ Hydrocephalus.</li> </ul>	<ul style="list-style-type: none"> <li>➤ Growth retardation.</li> <li>➤ Purpuric skin lesions.</li> </ul>

	Rubella	Toxoplasmosis	CMV
Other features	<ul style="list-style-type: none"> <li>➤ Growth retardation.</li> <li>➤ <u>HSM</u>.</li> <li>➤ Purpuric skin lesions.</li> <li>➤ 'Salt and pepper' chorioretinitis.</li> <li>➤ Microphthalmia.</li> <li>➤ Cerebral palsy.</li> </ul>	<ul style="list-style-type: none"> <li>➤ Anaemia.</li> <li>➤ <u>HSM</u>.</li> <li>➤ Cerebral palsy.</li> </ul>	<ul style="list-style-type: none"> <li>➤ Sensorineural deafness.</li> <li>➤ Encephalitis</li> <li>➤ Seizures.</li> <li>➤ Pneumonitis.</li> <li>➤ <u>HSM</u>.</li> <li>➤ Anaemia.</li> <li>➤ Jaundice.</li> <li>➤ Cerebral palsy.</li> </ul>

**Congenital rubella:**

- Sensorineural deafness
- Congenital cataracts

**Congenital toxoplasmosis:**

- Cerebral calcification
- Chorioretinitis

**NB:** Chorioretinitis is found in around 75% of patients with **congenital toxoplasmosis**.

**NB:** A form of 'salt and pepper' chorioretinitis is also seen in **congenital rubella** but this is not a common feature.

NB: A **positive rubella haemagglutination inhibition (HAI)** combined with a **negative rubella IgM** is consistent with:

- 1) Early acute infection with rubella
- 2) Previous vaccination, or
- 3) Previous rubella infection.

The rubella IgM may take several days to rise and the test should be repeated one to two weeks later.

**EX:** A 24-year-old woman consults her GP with a **one day history** of **fever** and a **macular rash**. She is 8 weeks pregnant and has not been immunised against rubella.

Lab: negative rubella IgM and a rubella haemagglutination inhibition (HAI) titre of 1:64.

What advice do you give the patient >>> **Repeat rubella IgM after 1-2 wks.**

## Vaccinations

**Live attenuated:** (It may carry a ☹️ **risk** to **immunocompromised** patients and **pregnant** ladies):

- 1) BCG
- 2) (MMR): Measles, mumps, rubella
- 3) Influenza (intranasal)
- 4) Oral polio
- 5) Oral rotavirus
- 6) Oral typhoid (the whole cell typhoid vaccine is no longer used in the UK).
- 7) Yellow fever

## **Inactivated preparations (Killed):**

- 1) Rabies
- 2) Influenza (IM)

## **Detoxified exotoxins:**

- Tetanus toxoid.

**Extracts / fragments of the organism/virus** produced by **recombinant DNA technology**:

- 1) Hepatitis B
- 2) Meningococcus, pneumococcus, haemophilus
- 3) Diphtheria
- 4) Pertussis ('acellular' vaccine)

### Notes:

- Influenza: different types are available, including whole inactivated virus, split virion (virus particles disrupted by detergent treatment) and sub-unit (mainly haemagglutinin and neuraminidase).
- Cholera: contains inactivated Inaba and Ogawa strains of *Vibrio cholerae* together with recombinant B-subunit of the cholera toxin.
- Hepatitis B: contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology.

Some individuals, particularly those that are **immunosuppressed**, are at risk if they are given **live** vaccines.

Inactivated vaccines are generally not dangerous but may be ineffective.

They are also at risk of severe manifestations to vaccines such as disseminated infection with bacillus Calmette-Guérin (BCG).

Those patients who receive **prednisolone 40 mg/day for more than a week** or who are on lower doses for more prolonged periods should be considered to be **immunosuppressed**.

Asthma alone is not a contraindication to vaccination even if patients are taking inhaled corticosteroids.

### Post-exposure prophylaxis

#### Hepatitis A:

- Human Normal Immunoglobulin (HNIG) or hepatitis A vaccine may be used depending on the clinical situation.

#### Hepatitis B:

- **HBsAg positive source:**
  - If the person exposed is a known responder to HBV vaccine then a booster dose should be given.
  - If they are in the process of being vaccinated or are a non-responder they need to have **hepatitis B immune globulin (HBIG) and the vaccine**.
- **Unknown source:**
  - For known responders the green book advises considering a booster dose of HBV vaccine.

- For known non-responders HBIG + vaccine should be given whilst those in the process of being vaccinated should have an accelerated course of HBV vaccine.

**Hepatitis C:**

- **Monthly PCR**
- If seroconversion >>> then interferon +/- ribavirin

**HIV:**

- **A combination of oral antiretrovirals** (e.g. Tenofovir, emtricitabine, lopinavir and ritonavir) **as soon as possible** (i.e. within 1-2 hours, but may be started **up to 72 hours** following exposure) **for 4 weeks**.
- **Serological testing at 12 weeks** following completion of post-exposure prophylaxis.
- Reduces risk of transmission by **80%**.

Post-exposure prophylaxis for HIV: oral antiretroviral therapy ASAP for 4 weeks
---

**Varicella zoster:**

- **VZIG for IgG negative pregnant women/immunosuppressed.**

**Estimation of transmission risk for single needle stick injury:**

Hepatitis B	<b>20-30%</b>
Hepatitis C	<b>0.5-2%</b>
HIV	<b>0.3%</b>

**Whooping cough (pertussis)**

It is caused by the bacterium **Bordetella pertussis**.

B. pertussis is a very small gram-negative aerobic coccobacillus that appears singly or in pairs.

Infection is characterised by paroxysms of coughing. **Lymphocytosis** is typically found.

The pertussis vaccine is estimated to be 63% to 94% effective in the diphtheria-pertussis-tetanus (DPT) shot. A **rare** complication is a **hemiseizure-hemiplegia**

**syndrome**, which is thought to be related to **post-immunisation hyperthermia** rather than direct neurological toxicity.

The incidence of pertussis is highest in **infants**, but it is also seen in **adolescents** and **adults**.

It is **infants under the age of 3 months** who are at the **highest risk** of severe complications, hospitalisation and death.

It is associated with **febrile convulsions** which are seen with **equal prevalence** to other childhood infectious diseases.

Although it is a bacterial disease, **antibiotics do not alter** the clinical course once the disease is established. Erythromycin, clarithromycin and azithromycin may be given however as they have been shown to reduce the period the patient is infective for.

### Botulism

It is caused by toxigenic strains of *Clostridium botulinum* and is usually caught from improperly tinned food, although it can also be contracted from **meat products** and **uncooked seafood**, and from **injecting abscesses**.

It causes diplopia, blurred vision, photophobia, bulbar palsy, ataxia and sudden cardiorespiratory failure with no GI symptoms.

The patient should be admitted at **ITU** and **intubated** early. **Antitoxin** needs to be given as quickly as possible before the patient has a cardiac arrest.

Botulism is usually diagnosed via **stool culture**.

### Encephalitis

Encephalitis may be caused by:

- 1) **Direct invasion** by a neurotoxic virus (encephalitis): caused by enteral viruses, HSV 1 and 2, varicella, CMV, EBV, respiratory viruses, human herpes virus 6 (HHV6), rubella or mumps.
- 2) **Post-infectious encephalopathy**: delayed brain swelling because of an immunological response to the antigen, i.e. a **neuroimmunological response**, caused by measles or **varicella zoster** (cerebellar ataxia).
- 3) Slow virus infection, for example, HIV or **subacute sclerosing pan encephalitis (SSPE)**.



### Histoplasmosis

It is caused by **Histoplasma capsulatum**, a dimorphic soil **fungus**.

It is a yeast type fungus which is endemic in **Southern USA** at Mississippi, Ohio and Missouri, it occurs particularly in areas which house large **bat** and **bird** populations.

Slowly progressing chronic form occurs in those who are fit and **immunocompetent**.

Those who are weak, very young or very old or **immunocompromised** tend to acquire a disseminated infection.

**Acute** infection causes glandular fever-type symptoms, malaise, anorexia, arthralgia, headache and erythema nodosum. It can cause a **TB-like illness** with cough, haemoptysis, dyspnoea and BHL with cavitary lesions by CXR. Sometimes hepatitis is associated.

**Disseminated** infection causes bilateral adrenal enlargement in 80% of cases and it can result in adrenal insufficiency.

**Diagnosis:** Adrenal biopsy or FNA with **Groccott stain** (Groccott-stained adrenal biopsy).

**TTT:** Itraconazole for 3-6 months.

**NB:** DD of **FUO (Fever of unknown origin)** and **bilateral adrenal swelling** is: **TB, Lymphoma** or **Histoplasmosis**.

**EX:** Pt 50 years old with FUO for 3 months with night sweat and weight loss, Abdominal CT shows bilateral adrenal swelling >>> ? **Histoplasmosis** >>> **Groccott-stained adrenal biopsy**.

### Swimmer's ear

C/O: severe otitis externa, earache, discharge and spreading superficial skin infection with history of swimming in the **hotel pool**.

It is caused by **Pseudomonas aeruginosa**.

So it is not responding to Augmentin.

More severe spreading infections occurs more commonly in **diabetic** cases.

TTT: local and systemic antibiotics with ENT surgeon consultation.

**NB:** Persistent pyrexia 3 days after commencing powerful broad spectrum antibiotics (Meronem+ Garamycin + Teicoplanin) raises the possibility of **fungal** infection like systemic candidiasis and aspergillosis >>> so add **Amphotericin B** (its liposomal form is less nephrotoxic).

**Oropharyngeal candidiasis** may be treated with **topical antifungal** agents (such as nystatin, clotrimazole, and amphotericin B oral suspension/lozenges).

**Oesophageal candidiasis** requires **oral or IV therapy** (usually with **Fluconazole** or Itraconazole for at least **14-21 days**) as topical therapy is inadequate.

## Diphtheria

**Pharyngeal diphtheria** presents with:

- 1) fever
- 2) sore throat
- 3) cervical lymphadenopathy, and
- 4) An adherent, grayish pharyngeal membrane.

The diphtheria toxin causes cardio- and neurotoxicity.

Treatment consists of antibiotic therapy and diphtheria antitoxin.

Diphtheria is caused by the Gram positive bacterium *Corynebacterium diphtheriae*

Pathophysiology:

- Releases an exotoxin encoded by a  $\beta$ -prophage
- Exotoxin inhibits protein synthesis by catalyzing ADP-ribosylation of elongation factor EF-2

Diphtheria toxin commonly causes a '**diphtheric membrane**' on **tonsils** caused by necrotic mucosal cells. Systemic distribution may produce necrosis of myocardial, neural and renal tissue.

Possible presentations:

- Recent visitors to Eastern Europe/Russia/Asia
- Sore throat with a 'diphtheric membrane'
- Bulky cervical lymphadenopathy
- Neuritis e.g. cranial nerves
- Heart block

**Exotoxins and endotoxins**

Exotoxins are secreted by bacteria whereas endotoxins are only released following lysis of the cell.

**Exotoxins:**

Exotoxins are generally released by Gram positive bacteria with the notable exceptions of *Vibrio cholerae* and some strains of *E. coli*. They may be classified into a number of different groups:

Superantigens (bridges the MHC class II protein on antigen-presenting cells with the T cell receptor on the surface of T cells resulting in massive cytokine release):

- *Staphylococcus aureus*: exotoxins lead to acute gastroenteritis (enterotoxins), toxic shock syndrome (TSST-1 superantigen) and staphylococcal scalded skin syndrome (exfoliatin)
- *Streptococcus pyogenes*: scarlet fever

AB toxins - ADP ribosylating:

- Diphtheria toxin inhibits elongation factor (EF-2) causing a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Systemic distribution may produce necrosis of myocardial, neural and renal tissue
- *Pseudomonas aeruginosa* produces exotoxin A which also inhibits EF-2
- **Cholera toxin** has two parts, A and B. B binds while **A** activates G protein, which activates **adenylate cyclase** (via  $G_s$ ) leading to increases in **cAMP** levels, which in turn leads to **increased chloride secretion** and reduced sodium absorption.
- Pertussis exotoxin inhibits  $G_i$  leading to increases in cAMP levels.

*Escherichia coli*:

- Heat labile: activates adenylate cyclase (via  $G_s$ ), increasing cAMP → watery diarrhoea
- Heat stable: activates guanylate cyclase, increasing cGMP → watery diarrhoea

Lockjaw is caused by *Clostridium tetani* neurotoxin (tetanospasmin) which blocks the release of GABA and glycine.

*Bacillus anthracis* produces oedema factor, a bacterial adenylate cyclase which increases cAMP.

*Clostridium perfringens* produces  $\alpha$ -toxin, a lecithinase, which causes gas gangrene (myonecrosis) and haemolysis.

*Clostridium botulinum* produces an exotoxin that blocks acetylcholine (ACh) release leading to flaccid paralysis.

*Shigella dysenteriae* produces Shiga toxin which inactivates 60S ribosome.

### **Endotoxins:**

Endotoxins are lipopolysaccharides that are released from Gram-negative bacteria such as *Neisseria meningitidis*.

# Neurology



### Transient Ischaemic Attack (TIA)

NICE issued updated guidelines relating to stroke and TIA.

They advocated the use of the **ABCD2** prognostic score for risk stratifying patients who've had a suspected TIA:

	Criteria	Points
<b>A</b>	Age $\geq$ 60 years	1
<b>B</b>	Blood pressure $\geq$ 140/90 mmHg	1
<b>C</b>	Clinical features: - Unilateral weakness. - Speech disturbance, no weakness.	2 1
<b>D</b>	Duration of symptoms: - $>$ 60 minutes. - 10-59 minutes.	2 1
<b>D</b>	Patient has Diabetes	1
<b>TOTAL</b>		<b>7</b>

This gives a total score ranging from **0 to 7**.

People who have had a suspected TIA who are at a higher risk of stroke (that is, with an **ABCD2 score of  $\geq 4$**  should have:

- 1) **Aspirin (300 mg daily) started immediately.**
- 2) Specialist assessment and investigation **within 24 hours** of onset of symptoms.
- 3) Measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.

If the **ABCD2 risk score is  $\leq 3$** :

- Specialist assessment **within 1 week** of symptom onset, including decision on brain imaging.
- If vascular territory or pathology is uncertain, refer for brain imaging.

People with **crescendo TIAs** (2 or more episodes in a wk) should be ttt as being at high risk of stroke, even though they may have an ABCD2 score of 3 or below.

Antithrombotic therapy:

- **Clopidogrel** is recommended first-line (as for patients who've had a stroke).
- Aspirin + dipyridamole should be given to patients who cannot tolerate clopidogrel.
- These guidelines may change following the CHANCE study (NEJM 2013; 369:11). This study looked at giving high-risk TIA patients **aspirin + clopidogrel for the first 90 days compared to aspirin alone**. 11.7% of aspirin only patients had a stroke over 90 days compared to 8.2% of dual antiplatelet patients.

Antiplatelets:

- TIA: **Clopidogrel**
- Ischaemic stroke: **Clopidogrel**

### **Stroke: management**

The Royal College of Physicians (RCP) and NICE guidelines:

Selected points relating to the management of acute stroke include:

- **Blood glucose, hydration, oxygen saturation and temperature** should be maintained within normal limits
- **Blood pressure should not be lowered in the acute phase** unless there are complications e.g. Hypertensive encephalopathy.
- **Aspirin 300mg orally or rectally** should be given **as soon as possible** if a haemorrhagic stroke has been excluded.
- With regards to **atrial fibrillation**, the RCP state: '**anticoagulants should not be started until brain imaging has excluded haemorrhage, and usually not until 14 days have passed from the onset of an ischaemic stroke**'.
- If the cholesterol is **> 3.5 mmol/l** patients should be commenced on a **statin**. Many physicians will delay treatment **until after at least 48 hours** due to the **risk of haemorrhagic transformation**.

**Thrombolysis:**

Thrombolysis should only be given if:

- It is administered **within 4.5 hours of onset of stroke symptoms** (the thrombolytic window) (unless as part of a clinical trial).
- Haemorrhage has been definitively excluded (i.e. Imaging has been performed).
- **Alteplase (tPA)** is currently recommended by NICE.

Stroke thrombolysis with tPA >> only consider if less than 4.5 hours and haemorrhage excluded.

The **National Institute of Neurological Disorders and Stroke (NINDS)** issued a protocol with inclusion and exclusion criteria for tPA:

**Their inclusion criteria were:**

- 1) Age over 18
- 2) Clinical diagnosis of acute ischaemic stroke
- 3) Known time of onset
- 4) CT scan consistent with diagnosis, and
- 5) Treatment can be given within 180 minutes (though some physicians treat after this period).

**Their exclusion criteria included:**

- 1) Intracranial haemorrhage on CT scan
- 2) Symptoms minor or improving
- 3) Active bleeding at any site
- 4) Gastrointestinal bleed in the last 21 days
- 5) Major surgery in last 14 days
- 6) History of intracranial bleed
- 7) Serious head injury in last 3 months
- 8) Pregnancy, or
- 9) Active pancreatitis.

**Secondary prevention:**

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole for prevention of further OVE (occlusive vascular events).

Recommendations from NICE include:

- **Clopidogrel** is now recommended by NICE ahead of combination use of aspirin plus dipyridamole modified release (MR) in people who have had an ischaemic stroke.



- Aspirin plus dipyridamole MR is now recommended after an ischaemic stroke only if clopidogrel is contraindicated or not tolerated, but treatment is no longer limited to 2 years' duration (i.e. it will be lifelong).
- Dipyridamole MR alone is recommended after an ischaemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with no limit on duration of treatment. (i.e. it will be lifelong).

**Secondary prevention of OVE:**

- Clopidogrel
- Aspirin plus dipyridamole MR
- Dipyridamole MR alone

Dipyridamole is not to be used in acute phase.

**EX:** Pt with ischemic stroke: at discharge from hospital after 14 days >> he should receive: (**Clopidogrel + Statin** If the cholesterol is **> 3.5**).

**With regards to carotid artery endarterectomy:**

- Current UK guidelines recommend endarterectomy for **symptomatic** patients with **greater than 70% stenosis**, based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET) which showed clear benefit. The endarterectomy should be performed **as soon as the patient is fit** for surgery, preferably **within 2 weeks of a TIA**.
- The benefit is **marginal** for **symptomatic** patients with **50-69% stenosis**, but may be greater in **male** patients. NICE recommends these patients are also considered for endarterectomy.
- There is significantly **less** benefit for **asymptomatic** patients, even those with **greater than 60% stenosis**.
- Patients with **less than 50%** stenosis should **not** be considered for carotid surgery.
- Recurrent stenosis can occur in 1-20% of patients following endarterectomy, and re-operation is needed in 1-3% of cases.
- All patients with suspected non-disabling stroke or TIA who are considered as candidates for carotid endarterectomy should have **carotid imaging within 1 week**.

**Indications for carotid endarterectomy:**

- 1) **Symptomatic** patients with **greater than 70%** stenosis (NASCET).
- 2) **Symptomatic** patients with **50-69%** stenosis.
- 3) **Asymptomatic** patients with **greater than 60%** stenosis.

In general,

- 1) **Symptomatic patients with greater than 50% stenosis**, and
- 2) **Healthy asymptomatic patients with greater than 60% stenosis**, warrant consideration for carotid endarterectomy.

**Carotid stenting** is increasingly being used as an alternative to endarterectomy. This is a less invasive revascularisation strategy, and uses an embolic protection device. There seems to be a similar early risk of death or stroke, and similar long-term benefits. Risk is higher in elderly patients, possibly due to vascular tortuosity and calcification. The procedure is currently indicated in selected cases, such as restenosis.

### Carotid artery dissection

The **two** commonest causes of **young onset stroke (less than 40 years)** are **cardio embolism** and **carotid artery dissection**.

**75%** of carotid dissections affect the **internal carotid artery** (that is, **extracranially**), and may be related to neck trauma or manipulation, although the cause is often difficult to identify.

The classic **triad** of symptoms of carotid dissection are:

- 1) **Unilateral (ipsilateral) headache**
- 2) **Ipsilateral Horner's** syndrome and
- 3) **Contralateral hemisphere** signs (aphasia, neglect, visual disturbance, and hemiparesis).

**Headache** is commonly **ipsilateral** to the **side** of the **carotid dissection**, and recurrence of the headache suggests extension or recurrence of the dissection.

The Horner's syndrome is caused by compression of the ascending sympathetic supply within the carotid sheath, and results in ptosis and miosis.

Anhydrosis is classically not present as the sympathetic supply to the sweat glands is along the external carotid plexus and is therefore spared.

**Ischaemic** neurological features (**transient** or completed **strokes**) are found in **30-80%** of patients presenting with carotid artery dissection.

Diagnosed by **Contrast arteriography of the neck vessels**

Management is aimed at preventing cerebral infarction, and is similar to that of acute stroke. Stenting can be used if there is ongoing ischaemia.

EX: A 21-year-old female presented with a sudden onset of **left sided head and neck pain**.

24 hours later she presents with **sudden onset of right hemiparesis**, facial weakness and **homonymous hemianopia** and **left Horner's syndrome**.

A CT brain showed a **left middle cerebral artery territory infarction**.

The most likely diagnosis? **Lt Carotid artery dissection**

**NB: Migrainous stroke** usually affects the **posterior** circulation (posterior cerebral artery territory is the commonest).

**NB:** A thrombotic event resulting from **cardio embolism** or **Antiphospholipid syndrome** would usually **only** affect **intracranial** vessels and therefore a **Horner's syndrome** would be **unusual**.

#### **Neurosurgical intervention in acute ischaemic stroke:**

- 1) Patients who are **under 60 years** of age with **large cerebral infarctions** arising in the **MCA territory** should be considered for **decompressive hemicraniectomy** which is removing part of the skull in order to reduce ICP and should be carried out within 48 hours of the index event.
- 2) A **massive cerebellar infarction** or evidence of **hydrocephalus** or **brainstem compression**.

#### **Stroke by anatomy**

Site of the lesion	Associated effects
Anterior cerebral artery (ACA)	<ul style="list-style-type: none"> <li>-Contralateral hemiparesis and sensory loss, <u>lower</u> extremity &gt; upper.</li> <li>-Disconnection syndrome (Akinetic mute patient).</li> </ul>
Middle cerebral artery (MCA)	<ul style="list-style-type: none"> <li>-Contralateral hemiparesis and sensory loss, <u>upper</u> extremity &gt; lower.</li> <li>-Contralateral homonymous hemianopia.</li> <li>-Aphasia (Wernicke's).</li> <li>-Gaze abnormalities.</li> </ul>

Site of the lesion	Associated effects
Posterior cerebral artery (PCA)	<ul style="list-style-type: none"> <li>- Pure hemisensory loss</li> <li>- Contralateral homonymous hemianopia with macular sparing.</li> <li>- Visual agnosia.</li> <li>- Disorders of reading (alexia, dyslexia)</li> <li>- Disconnection syndrome.</li> </ul>
Weber's syndrome (branches of the PCA that supply the midbrain)	<ul style="list-style-type: none"> <li>- Ipsilateral CN III palsy.</li> <li>- Contralateral weakness.</li> </ul>
Posterior inferior cerebellar artery (= lateral medullary syndrome), (=Wallenberg syndrome)	<ul style="list-style-type: none"> <li>- Ipsilateral cerebellar: Ataxia, nystagmus.</li> <li>- Ipsilateral signs of Horner's syndrome.</li> <li>- Ipsilateral loss of corneal reflex</li> <li>- Ipsilateral facial loss of pinprick sensation</li> <li>- <b>Contralateral</b> signs of <b>spinothalamic</b> sensory loss of the limb/torso <b>pain and temperature loss.</b></li> </ul>
Anterior inferior cerebellar artery (lateral pontine syndrome)	Symptoms are similar to Wallenberg's (see above), but add: Ipsilateral: facial paralysis and deafness
Pontine	<ul style="list-style-type: none"> <li>- 6 th nerve palsy: horizontal gaze palsy.</li> <li>- 7 th nerve palsy</li> <li>- Contralateral hemiparesis.</li> </ul>
Retinal/ophthalmic artery	Amaurosis fugax

Site of the lesion	Associated effects
Basilar artery	<b>'Locked-in' syndrome:</b> Pt is awake but is unable to respond in anyway except by vertical gaze and blinking (lesion is in ventral <b>pons</b> ).

**Lacunar strokes:**

- Present with either isolated hemiparesis, hemisensory loss or hemiparesis with limb ataxia.
- Strong association with HTN
- Common sites include the basal ganglia, thalamus and internal capsule.

**Lateral medullary syndrome (Wallenberg's syndrome)**

It occurs following occlusion of the **posterior inferior cerebellar artery (PICA)**.

**Cerebellar features:** Ataxia and nystagmus.

**Brainstem features:**

- 1) **Ipsilateral:** dysphagia, facial numbness, cranial nerve palsy e.g. **Horner's**
- 2) **Contralateral: limb sensory loss** (pyramidal tract signs).

**Lateral medullary syndrome** >> PICA lesion >> Ipsilateral Cerebellar signs + Ipsilateral Horner's + Contralateral limb sensory loss.

**Brown-Sequard syndrome**

It is a loss of sensation and motor function that is caused by the **lateral hemisection of the spinal cord**.

**Ipsilateral** signs include **pyramidal** weakness and **dorsal column** dysfunction (joint position and light touch) and **contralateral** signs include **spinothalamic** dysfunction (pinprick and temperature).

Features:

- 1) Ipsilateral loss of fine touch, vibration and proprioception.
- 2) Ipsilateral hyperreflexia and extensor planter reflex.
- 3) **Contralateral** loss of **pain and temperature** sensation.
- 4) Segmental anaesthesia at the level of the lesion.

Complete syndrome picture is rare and many patient may only exhibit some features.

Causes:

- Trauma is the common cause.
- Demyelination due to multiple sclerosis.
- Any lateral cord lesion (Ischaemia, haemorrhage, granuloma, tumour etc).

### **Syringomyelia**

Overview:

- Development of cavity (**syrinx**) within the spinal cord that produce progressive myelopathy.
- Symptoms begins insidiously in adolescence or early adulthood, progress irregularly, and may undergo spontaneous arrest for several years; most patients acquire a cervical-thoracic scoliosis.
- If extends into **medulla** then termed **syringobulbia**
- Strongly associated (> 50%) with the **Arnold-Chiari malformation**.

Features:

- May be **asymmetrical initially**.
- **Slowly progressives**, possibly over years.
- Motor: **wasting** and **weakness** of arms.
- Sensory: **Spinothalamic** sensory loss (**pain** and **temperature**).
- **Loss of reflexes**, bilateral upgoing plantars.
- Also seen: Horner's syndrome.

<b>Syringomyelia &gt;&gt; Spinothalamic sensory loss (pain and temperature).</b>
--

<b>EX:</b> A 35-year-old woman presents with <b>pains in the right arm</b> . She has <b>wasting</b> and <b>weakness</b> of the intrinsic muscles of the right hand, <b>absent tendon reflexes</b> in the right arm and <b>impaired pinprick sensation</b> in the right hand and forearm.
--

The most likely diagnosis >>> <b>Syringomyelia</b>
--

Localization of the lesion:

- At syrinx (there is anterior horn cell involvement) → LMNL weakness.
- At central decussating fibers (spinothalamic tract) → dissociated sensory loss with late development of neuropathic arthropathy.
- At corticospinal tracts below the level of the syrinx → spastic paraplegia.

**MRI** is the investigation of choice

Myelography used to confirm the diagnosis but was associated with more deterioration.

**Transverse myelitis (TM)**

It is an **inflammatory lesion** that can affect the cord.

Constitutional symptoms such as headache and fever are common as is pain.

Signs are indistinguishable from those caused by cord compression and again **all sensory aspects are equally affected** with no sparing of proprioception.

The clinical signs are caused by an **interruption in ascending and descending pathways in the transverse plane of the spinal cord**.

**A sensory level is characteristic.**

**Midline or dermatomal neuropathic pain** can be present.

**Urinary** incontinence or retention, **bowel** incontinence or constipation, and **sexual** dysfunction are common but vary in severity.

These signs develop over hours to days, and are usually **bilateral**.

There are a variety of causes, but it most often occurs as an **autoimmune** phenomenon after an infection or vaccination, or as a result of direct infection, an underlying systemic autoimmune disease, or an acquired demyelinating disease. For a significant proportion of cases **no cause is found**.

**MRI** is indicated to rule out the presence of **structural** lesions, and determine the presence of **myelitis** which **enhances with gadolinium** in the acute phase. There may be more than one area of myelitis, and the lesions usually span at least two vertebral segments. **In the acute phase the MRI may be normal.**

**Treatment** in the acute phase aims to halt the progression and initiate resolution of the inflammatory cord lesion. **High doses Corticosteroids IV** are first line. **Plasma exchange** can be given to those who fail to respond. Patients with demyelinating disease can be started on long term immunosuppression.

The **prognosis** is highly **variable**, and improvement can take 3 months and longer to develop.

**50% to 70%** of patients **have partial or complete recovery** 😊

A rapidly progressive course, severe weakness, hypotonia and areflexia are predictors of poor prognosis.

### **Subclavian Steal Syndrome**

It is associated with retrograde flow in the vertebral artery due to proximal subclavian artery stenosis.

Neurological symptoms are precipitated by vigorous exercise with the arm above the head, such as painting a wall.

Diagnosis is often confused with TIA or epilepsy.

Duplex US and **MRA** are the investigations of choice.

TTT: Endarterectomy and stenting.

### **Subacute Combined Degeneration of spinal cord (SCD)**

It is also known as Lichtheim's disease.

It refers to **degeneration** of the **posterior** and **lateral** columns of the spinal cord as a result of Vit B12 deficiency (most common), Vit E deficiency or Friedrich's ataxia.

It is usually associated with pernicious anaemia.

Features:

- Patchy losses of myelin in the dorsal and lateral columns.
- Present with progressive weakness of legs, arms, trunk, tingling and numbness.
- **Visual** and **mental** changes may also be present.
- **Bilateral spastic paresis** with diminished **pressure**, **vibration** and **touch** sense.
- **Positive Babinski** sign may be seen.
- **Extensor plantars with absent ankle reflexes**

Prolonged deficiency of Vit B12 (**>3 months**) leads to **irreversible** nervous system damage.

If someone is deficient on Vit B12 and folic acid, the **Vit B12 deficiency should be treated first** to avoid precipitating SCD of the cord.



TTT with Vit B12 results in partial to full recovery, depending on the duration and extent of neurodegeneration.

### **Absent ankle jerks**

**Absent ankle jerks** may occur in conditions associated with neuropathy:

- 1) **B12 deficiency,**
- 2) **SLE,**
- 3) **Tabes dorsalis (Syphilis)**
- 4) **Cerebrotendinous xanthomatosis**

**Cerebrotendinous xanthomatosis** is an inherited condition, associated with accumulation of cholesterol in tissues including brain, peripheral nerve and tendons which produces a clinical picture of:

- Early onset dementia
- Gait ataxia
- Loss of vibration sense
- Cataracts
- Large tendon xanthomata.
- There is a deficiency in sterol storage, and diagnosis is based on **high serum (and tendon) cholestANOL**. BUT Serum cholesterol may be normal or low.
- It is eminently treatable by the oral chenodeoxycholic acid.

**EX:** A 39-year-old woman is found to have **absent ankle jerks** and **gait disturbance** >>> so should check: **ANA, B12, VDRL, Cholestanol levels**

### **Extensor plantars and absent ankle jerks (Lesions that produce both UMNL and LMNL)**

Typically caused by **lesion** producing **both** **UMNL** (extensor plantars) and **LMNL** (absent ankle jerk) signs.

Causes:

- 1) **SCD** (Subacute combined degeneration of the cord)
- 2) **MND** (Motor neuron disease)
- 3) **Friedreich's ataxia**
- 4) **Syringomyelia, Syringobulbia.**
- 5) **Taboparesis (syphilis)**
- 6) **Conus medullaris lesion**

### Spastic paraparesis

Spastic paraparesis describes an **UMN** upper motor neuron pattern of weakness in the lower limbs. (i.e. weakness in both lower limbs, increased tone in both legs and brisk reflexes with normal upper limbs).

Causes:

- 1) **Cord compression:** trauma, tumour
- 2) **Parasagittal meningioma**
- 3) Demyelination e.g. **multiple sclerosis**
- 4) **Transverse myelitis** e.g. **HIV**
- 5) **Syringomyelia**
- 6) **Hereditary spastic paraplegia**
- 7) Tropical spastic paraparesis
- 8) Osteoarthritis of the cervical spine

### Brain lesions (Gross anatomy):

#### Frontal lobes lesions:

- 1) **Expressive (Broca's) aphasia:** located on the **posterior** aspect of the frontal lobe, in the inferior frontal gyrus. Speech is non-fluent, laboured, and halting. (I.e. difficulty in finding the right words whilst speaking).
- 2) Anosmia.
- 3) Changes in personality
- 4) Disinhibition.
- 5) Primitive reflexes (positive grasp, pout and palmomental reflexes).
- 6) Urinary and faecal incontinence
- 7) Perseveration (repeatedly asking same question or doing same task).
- 8) **Inability to generate a list rapidly** (For example name animals in 60 seconds or words beginning with the letter F, etc.).
- 9) Difficulties with executive skills

**Frontal lobe dementia** is a common neurodegenerative condition. It usually affects patients of **45-65 years old**.

**50%** of patients presenting with **status epilepticus** (with **no** previous history of seizures) have **frontal lobe tumour**.

**Parietal lobe lesions:**

- 1) Sensory inattention.
- 2) **Neglect.**
- 3) **Apraxias** (loss of the ability to execute learned purposeful movements).
- 4) **Astereognosis** (tactile agnosia) (inability to recognize object by feeling)
- 5) **Inferior homonymous quadrantanopias**
- 6) **Gerstmann's syndrome** (lesion of dominant parietal):
  - I. **Alexia** (inability to read), قراءة
  - II. **Acalculia** (inability to perform mental arithmetic calculation), العد
  - III. **Agraphia** (difficulty in writing), كتابة
  - IV. **Dyslexia** (inability to recognise letters or words) معرفة الحروف
  - V. **Finger agnosia** (difficulty in identifying fingers and naming them)
  - VI. **Right-left disorientation.**

**Temporal lobe lesion:**

- 1) **Wernicke's (receptive) aphasia:** this area 'forms' the speech before 'sending it' to Brocas area. Lesions result in word substitution, neologisms but speech remains fluent.
- 2) **Superior homonymous quadrantanopias.**
- 3) **Auditory agnosia.**
- 4) **Prosopagnosia** (difficulty recognising faces).
- 5) **Memory impairment.**

**Occipital lobe lesions:**

- 1) **Homonymous hemianopia** (with **macula sparing**)
- 2) **Cortical blindness** (blindness due to damage to the visual cortex, may present as Anton syndrome: there is blindness but the patient is unaware or denies blindness).
- 3) **Visual agnosia** (seeing but not perceiving objects- it is different to neglect since in agnosia the objects are seen and followed but cannot be named).

<p><b>Unilateral occipital lobe lesions</b> (left or right) cause contralateral hemianopia or <b>quadrantanopsia</b>, visual illusions and elementary visual hallucinations.</p>
--

**Cerebellum lesions:**

- Midline lesions: gait and truncal ataxia.
- Hemisphere lesions: intention tremor, past pointing, dysdiadokinesis, nystagmus.

**More specific areas:**

Area	Associated conditions
Medial thalamus and mammillary bodies of the hypothalamus	Wernicke and Korsakoff syndrome
Subthalamic nucleus of the basal ganglia	Hemiballism
Striatum (caudate nucleus) of the basal ganglia	Huntington chorea
Substantia nigra of the basal ganglia	Parkinson's disease
Amygdala	Kluver-Bucy syndrome (hypersexuality, hyperorality, hyperphagia, visual agnosia)

Dorsal column dysfunction: Joint position and light touch.

Spinothalamic dysfunction: Pinprick and temperature.

Thalamic and frontal lobe infarction do not cause visual field defects.

### Visual field defects

Visual field defect is a manifestation of the following pathology:

- **Occipital** lobe (**homonymous** hemianopia)
- **Temporal** lobe (**superior quadrantanopia**) or
- **Parietal** lobe (**inferior quadrantanopia**).

The main points for the exam are:

- **Right homonymous hemianopia** means visual field defect to the right, i.e. Lesion of left optic tract.
- **Incongruous** defects = optic tract lesion
- **Congruous** defects = optic radiation lesion or occipital cortex

A **congruous** defect (defect is approximately the same in each eye) simply means complete or symmetrical visual field loss and conversely an **incongruous** defect is incomplete or asymmetric.

#### Homonymous hemianopia:

- **Incongruous** defects: lesion of **optic tract**.
- **Congruous** defects: lesion of **optic radiation** or **occipital cortex**.
- **Macula sparing**: lesion of occipital cortex.

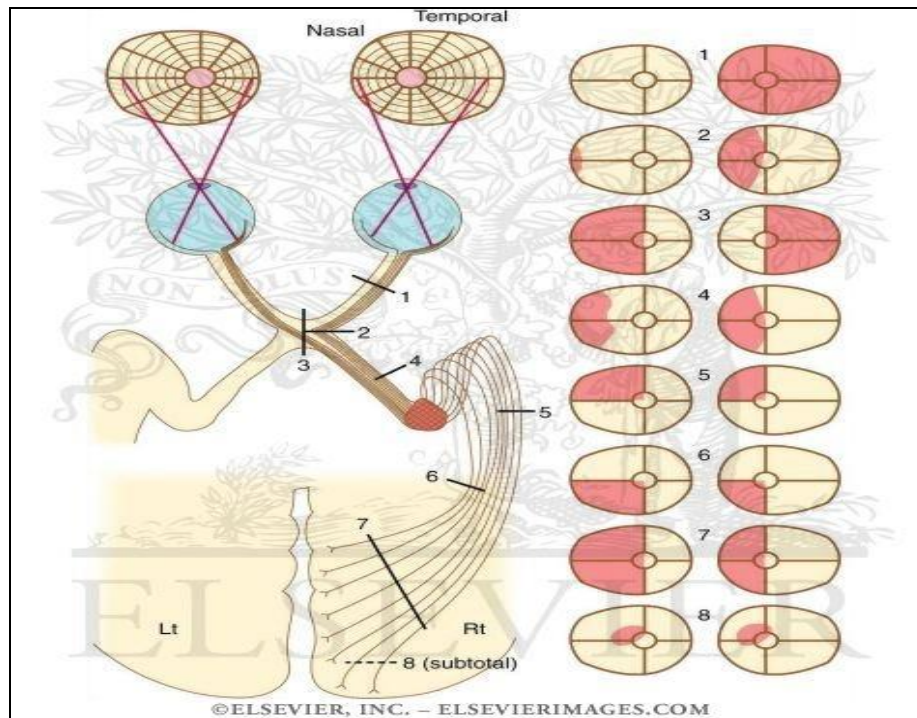
EX: Left congruous homonymous hemianopia >> lesion in Right occipital cortex.

#### Homonymous quadrantanopias:

- **PITS** (Parietal-Interior, Temporal-Superior).
- **Superior**: lesion of **temporal** lobe.
- **Inferior**: lesion of **parietal** lobe.

#### Bitemporal hemianopia:

- Lesion of **optic chiasm**.
- **Upper** quadrant defect > lower quadrant defect = **inferior** chiasmal compression, commonly a **Pituitary tumour**.
- **Lower** quadrant defect > upper quadrant defect = **superior** chiasmal compression, commonly a **Craniopharyngiomas**.



## Nystagmus

It is defined as involuntary oscillations of the eyes.

This may be **pendular** when the oscillations are equal in rate and amplitude, or **jerking** when there are quick and slow phases (the quicker phase is used to define the direction).

### Causes:

- 1) Visual disturbances.
- 2) Labyrinth lesions.
- 3) The central vestibular connections.
- 4) Brain stem lesion.
- 5) Cerebellar lesion.

### Types:

- Nystagmus which changes with the direction of the gaze: involvement of vestibular nuclei.
- Pendular: mostly due to loss of macular vision, but could be in diffuse brain stem lesions.
- Jerking regardless of the direction of gaze: labyrinthine or cerebellar lesion.
- Jerking on lateral gaze, and fast in the direction of gaze: brain stem or cerebellar lesion.
- Nystagmus confined to one eye: nerve or muscle lesion, or medial longitudinal bundle (MLB) lesion.

- Nystagmus restricted to the abducting eye on lateral gaze (ataxic nystagmus): lesion of the MLB between mid-brain and pons as in multiple sclerosis (MS).
- Nystagmus occurring on **upward** gaze with the fast component upwards (upbeat nystagmus) may be due to a lesion in the mid-brain at the level of the superior colliculus.
- **Downbeat** nystagmus (fast phase downwards) suggests a lesion in the lower part of the medulla. It is therefore typical of the Arnold-Chiari malformation.
- Wernicke's encephalopathy or thiamine deficiency is a rare cause of downbeat nystagmus.

<b>Upbeat</b> nystagmus:	Cerebellar vermis lesions.
<b>Downbeat</b> nystagmus-foramen magnum lesions:	<u>Arnold-Chiari malformation.</u>

**MLB**→coordinate lateral rectus of one side with medial rectus of the other side.

**Miosis** (small pupil): causes:

- 1) **Horner's syndrome**
- 2) **Argyll-Robertson pupil** عين العاهرة
- 3) Pontine haemorrhage
- 4) Congenital
- 5) Senile miosis
- 6) Drugs:
  - **Opiates**
  - **Organophosphate toxicity**
  - Parasympathomimetics: pilocarpine.

**Argyll-Robertson pupil**: small irregular pupils that do not react to light but react to accommodation.

Referred to as the “**Whore’s Eye**” because of the association with **tertiary syphilis** and because of the convenient **mnemonic** that, like a **prostitute**, they “**can accommodate but do not react**”.

**Another mnemonic** used for the Argyll-Robertson Pupil (**ARP**) is Accommodation Reflex Present (**ARP**) but Pupillary Reflex Absent (**PRA**).

Causes: Multiple sclerosis, sarcoidosis, DM.

## Horner's syndrome

Features:

- 1) **Ptosis.**
- 2) **Miosis** (small pupil).
- 3) **Anhydrosis** (loss of sweating one side).
- 4) **Enophthalmos:** (sunken eye): (in reality the appearance is due to a narrow palpebral aperture rather than true Enophthalmos).

Causes: (STC)

Central lesions	Pre-ganglionic lesions	Post-ganglionic lesions
Anhydrosis of the face, arm and trunk	Anhydrosis of the <b>face</b>	<b>No anhydrosis</b>
<b>Stroke</b> <b>Syringomyelia</b> Multiple sclerosis Tumour Encephalitis	Pancoast's tumour Thyroidectomy Trauma Cervical rib	<b>Carotid artery dissection</b> <b>Carotid aneurysm</b> <b>Cavernous sinus thrombosis</b> <b>Cluster headache</b>

Horner's syndrome - **Anhydrosis** determines site of lesion:

- Head, arm, trunk = central lesion: stroke, Syringomyelia.
- Just face = pre-ganglionic lesion: Pancoast's, cervical rib.
- Absent = post-ganglionic lesion: carotid artery.

Distinguishing between causes:

- Heterochromia (difference in iris colour) is seen in congenital Horner's
- Anhydrosis: see before.



## Ptosis

Ptosis may be unilateral or bilateral.

Causes of <b><u>bilateral</u></b> ptosis:	Causes of <b><u>unilateral</u></b> ptosis, as bilateral causes plus:
<ol style="list-style-type: none"> <li>1) <b>Myotonic dystrophy.</b></li> <li>2) <b>Myasthenia gravis</b></li> <li>3) <b>Syphilis.</b></li> <li>4) <b>Congenital.</b></li> </ol>	<ol style="list-style-type: none"> <li>1) <b>Horner's</b></li> <li>2) <b>Third nerve palsy</b></li> </ol>

Ptosis is much more common in myasthenia gravis than Lambert-Eaton syndrome

## Third nerve III palsy

Features:

- 1) **Eye is deviated 'down and out'.**
- 2) **Ptosis.**
- 3) **Mydriasis** (Pupil may be dilated) (sometimes called a 'surgical' third nerve palsy).
- 4) **Pain only if** due to a posterior communicating artery aneurysm.

Ptosis + **Miosis** (Constricted pupil) >>> **Horner's Syndrome**

Ptosis + **Mydriasis** (Dilated pupil) >>> **3 rd. Nerve palsy**

Causes:

- DM
- Vasculitis e.g. temporal arteritis, SLE
- False localizing sign due to uncus herniation through tentorium if raised ICP
- **Posterior communicating artery aneurysm (PCAA)** (pupil dilated)
- **Cavernous sinus thrombosis**
- **Weber's syndrome:** Ipsilateral third nerve palsy with contralateral hemiplegia -caused by midbrain strokes (cerebral peduncle).
- Other possible causes: amyloid, multiple sclerosis

\*This term is usually associated with sixth nerve palsies but it may be used for a variety of neurological presentations

**Painful third nerve palsy = posterior communicating artery aneurysm** (i.e. EX. Third nerve palsy with headache and meningism >>> should exclude posterior communicating artery aneurysm).

## Facial nerve

**Supply:** 'face, ear, taste, and tear':

- 1) **Face:** muscles of facial expression.
- 2) **Ear:** nerve to stapedius muscle >> paralysis >> Hyperacusis.
- 3) **Taste:** supplies anterior two-thirds of tongue.
- 4) **Tear:** parasympathetic fibres to lacrimal glands, also salivary glands >> Overflow of tears may occur but hyperlacrimation does not.

**Causes of unilateral facial nerve palsy:**

UMNL	LMNL
<b>Stroke</b>	<ul style="list-style-type: none"> <li>- Bell's palsy.</li> <li>- Ramsay-Hunt syndrome (due to HZV).</li> <li>- Acoustic neuroma.</li> <li>- Parotid tumours.</li> <li>- Multiple sclerosis (may also cause an UMN palsy).</li> <li>- HIV.</li> <li>- DM.</li> </ul>

**Causes of bilateral facial nerve palsy:**

- 1) **Sarcoidosis**
- 2) GBS.
- 3) MG.
- 4) Polio.
- 5) **Lyme** disease.
- 6) Bilateral Bell's palsy.

**LMN vs. UMN:**

- **Upper** motor neuron lesion '**spares**' **upper** face i.e. forehead
- **Lower** motor neuron lesion affects **all** facial muscles

Facial palsy + convergent squint → lesion is in **pons** as VI th is encircled by VII.

**Bell's palsy**

Bell's palsy may be defined as an acute, unilateral, idiopathic, facial nerve paralysis.

The aetiology is unknown although the role of the HSV has been investigated previously.

Features:

- **Lower motor neuron facial nerve palsy** i.e. forehead affected.
- Patients may also notice **post-auricular pain** (may precede paralysis), altered taste, dry eyes, **hyperacusis (present in 30% of cases)**.
- You need to be confident that there are no features of Guillain-Barré (test reflexes), or brain stem vascular disease or space occupying lesion.

Management:

- In the past a variety of treatment options have been proposed including no treatment, prednisolone only and a combination of acyclovir and prednisolone.
- Following a National Institute for Health randomised controlled trial it is now recommended that **prednisolone 25mg bid for 10 days** should be prescribed for patients **within 72 hours of onset** of Bell's palsy. Adding in acyclovir gives no additional benefit.
- **Eye care** is important - prescription of artificial tears and eye lubricants should be considered.

Prognosis:

- If untreated around 15% of patients have permanent moderate to severe weakness.

N.B: **Upper** motor neuron lesion of facial nerve '**spares**' **upper** face

N.B: A vesicular rash around the ear would suggest a diagnosis of Ramsey Hunt syndrome.

### Parkinson's disease: features

It is a progressive neurodegenerative condition caused by **degeneration** of **dopaminergic** neurons in the **substantia nigra (SN)**.

**Mutations** in either the **parkin gene** or **UCHL1** lead to **impaired protein degradation**.

This results in a classic **triad** of features: **bradykinesia**, **tremor** and **rigidity**.

The symptoms of Parkinson's disease are characteristically **asymmetrical**.

**Asymmetrical** symptoms (tremors) point towards a diagnosis of **idiopathic Parkinson's disease** rather than **Parkinsonism of another cause** e.g. **Drug-induced Parkinsonism**.

Epidemiology:

- Around twice as common in **men**
- Mean age of diagnosis is **65** years

#### 1) Bradykinesia:

- Poverty of movement also seen, sometimes referred to as **hypokinesia**.
- **Short, shuffling steps** with **reduced arm swinging**
- Difficulty in initiating movement

#### 2) Tremor:

- Typically **'pill-rolling'**, i.e. in the thumb and index finger
- Most marked at **rest**, with **low** frequency **3-5 Hz**
- **Worse** when stressed or tired and with levodopa

#### 3) Rigidity:

- **Lead pipe**
- **Cogwheel**: due to superimposed tremor

#### Other characteristic features:

- 1) **Mask-like facies**
- 2) **Flexed posture**
- 3) **Micrographia**
- 4) **Drooling of saliva**

- 5) Psychiatric features: **depression** is the most common feature (affects about **40%**); dementia, psychosis and sleep disturbances may also occur.
- 6) Impaired olfaction.
- 7) REM sleep behaviour disorder.

**NB:** **Diplopia** is not common in Parkinson's disease and may suggest an alternative cause of Parkinsonism such as **progressive supranuclear palsy**.

**NB:** Difficulty in initiating movement (bradykinesia), postural instability and unilateral symptoms (initially) >>> are typical of Parkinson's.

### **Causes of Parkinsonism:**

- 1) Parkinson's disease
- 2) Drug-induced e.g. antipsychotics, metoclopramide - see below
- 3) Progressive supranuclear palsy
- 4) Multiple system atrophy
- 5) **Wilson's disease**
- 6) Post-encephalitis
- 7) Dementia pugilistica (secondary to chronic head trauma e.g. boxing)
- 8) Toxins: carbon monoxide, Carbon disulphide, MPTP (methyl-phenyl tetrahydropyridine), Manganese and cycad nut

### **Drug-induced Parkinsonism:**

- Phenothiazines: e.g. chlorpromazine, prochlorperazine
- Butyrophenones: haloperidol, droperidol
- Metoclopramide

It has slightly different features to Parkinson's disease:

- **Motor** symptoms are generally **rapid onset** and **bilateral**.
- Rigidity and rest tremor are uncommon.

N.B: Domperidone does not cross the blood-brain barrier and therefore does not cause extra-pyramidal side-effects.

**NB:** **Anticholinergic** treatment (for example, benzhexol) is the treatment of choice for **tremor** predominantly Parkinson's disease.

**L-dopa** and **dopamine agonists** are the treatment of choice for **bradykinesia** and **rigidity**.

**Parkinson's disease (PD): management**

Currently accepted practice in the management of patients with Parkinson's disease (PD) is **to delay treatment until the onset of disabling symptoms** and **then to introduce a dopamine receptor agonist**.

**1) Dopamine receptor agonists:**

- Favoured for Pt. >75 Yrs. old.
- E.g. Bromocriptine, Cabergoline, Apomorphine, Ropinirole.
- **Ergot-derived dopamine receptor agonists** (Bromocriptine, Cabergoline, and Pergolide) have been associated with **pulmonary, cardiac and retroperitoneal fibrosis**.

**Ropinirole** is the **least** associated with tissue fibrosis.

**Ropinirole** is a **non-ergot** derived dopamine agonist licensed for ttt of Parkinsonism & restless leg syndrome.

It is a reasonable choice for **first line therapy** in **younger** patients.

- The Committee on Safety of Medicines advice that an echocardiogram, ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored.
- Patients should be warned about the potential for dopamine receptor agonists to cause **impulse control disorders** and **excessive daytime somnolence**.
- More likely than levodopa to cause **hallucinations** in older patients. **Nasal congestion** and **postural hypotension** are also seen in some patients.
- Dopamine agonists are thought to be associated with **less** on/off phenomena than L-Dopa based therapy and are seen as a reasonable choice for **first line therapy** in **younger patients**.

**Pergolide** was withdrawn from the US market in March 2007 due to concern regarding increased incidence of **valvular dysfunction**

**2) Levodopa:**

- **Favoured for Pt. < 75 Yrs. old.**
- If the patient is elderly, levodopa is sometimes used as an initial treatment.
- Usually combined with a **decarboxylase inhibitor** (e.g. Carbidopa or benserazide) to prevent peripheral metabolism of levodopa to dopamine.
- Dopa-decarboxylase inhibitors reduce the extracerebral complications of L-dopa therapy. These include nausea, vomiting, postural hypotension and cardiac arrhythmias.

- Reduced effectiveness with time (usually by 2 years).
- Unwanted effects:
  - 1) **Dyskinesia** (involuntary writhing movements).
  - 2) **'On-off' effect**.
  - 3) **Psychosis**, drowsiness.
  - 4) **Postural hypotension**
  - 5) **Cardiac arrhythmias**
  - 6) Dry mouth, anorexia, nausea and vomiting.
  - 7) Reddish discolouration of urine upon standing.
- Not use in neuroleptic induced Parkinsonism.

### **3) MAO-B (Monoamine Oxidase-B) inhibitors:**

- e.g. Selegiline.
- Inhibits the breakdown of dopamine secreted by the dopaminergic neurons.

### **4) Amantadine:**

- Mechanism is not fully understood, probably increases dopamine release and inhibits its uptake at dopaminergic synapses.
- SE: include ataxia, slurred speech, confusion, dizziness and livedo reticularis.

### **5) COMT (Catechol-O-Methyl Transferase) inhibitors:**

- e.g. Entacapone, tolcapone.
- COMT is an enzyme involved in the breakdown of dopamine, and hence may be used as an adjunct to levodopa therapy.
- Used in conjunction with levodopa in patients with established PD.

### **6) Antimuscarinics:**

- Block cholinergic receptors.
- Now used more to treat **drug-induced Parkinsonism** (i.e. Parkinsonism secondary to antipsychotic medications used in ttt of schizophrenia) rather than idiopathic Parkinson's disease.
- Also used in ttt of extrapyramidal symptoms (EPS) (Acute dystonic-dyskinetic reactions) of metoclopramide antiemetic.
- Help **tremor** and rigidity
- E.g. Benzotropine, Procyclidine, Trihexyphenidyl (Benzhexol).

## Progressive Supranuclear Palsy (PSP)

Overview:

- It is also known as **Steele-Richardson-Olszewski Syndrome (SROS)**
- A **'Parkinson Plus' syndrome**
- It is degenerative disease with gradual deterioration and death of selected areas of the brain. About 6 people per 100,000.

Features: (**Triad**):

- 1) **Parkinsonism**
- 2) **Impairment of vertical gaze** due to supranuclear paralysis of upward and downward gaze (the down gaze worse than up gaze - patients may complain of difficulty reading or descending stairs)
- 3) **Cognitive impairment**
- 4) **Falls**
- 5) **Slurring of speech**

Management:

- **Poor response to L-dopa**

<b>PSP (Triad):</b> Parkinsonism+ impairment vertical gaze + Cognitive impairment
---

## Multiple system atrophy

**Shy-Drager syndrome** is a type of multiple system atrophy.

Features:

- 1) **Parkinsonism**
- 2) **Cerebellar signs**
- 3) **Autonomic disturbance** (disturbance of sphincter control, atonic bladder with urinary retention , impotence, anhidrosis and postural hypotension)

The Parkinson's symptoms associated with multi-system atrophy respond **poorly** to dopamine agonists or L-dopa, in contrast to idiopathic Parkinson's.

Urinary retention can be managed with an **indwelling catheter** if required,

Postural hypotension managed with **support stockings ± mineralocorticoids**



## **Dementia**

Dementia is thought to affect over 700,000 people in the UK and accounts for a large amount of health and social care spending.

The **most common cause of dementia** in the UK is **Alzheimer's disease** followed by **vascular** and **Lewy body dementia**. They may coexist.

Features:

- Diagnosis can be difficult and is often delayed.
- The **Mini-Mental State Examination (MMSE) score** is widely used. A score of **≤ 24 out of 30** suggests dementia.

Management:

- 1) In primary care a **blood screen** is usually sent to exclude reversible causes (e.g. Hypothyroidism).

NICE recommend the following tests: **CBC**, **U&E**, **LFTs**, **Ca++**, **glucose**, **TFTs**, **Vit.B12** and **folate** levels. Patients are now commonly referred on to old-age psychiatrists (sometimes working in 'memory clinics').

- 2) In secondary care **neuroimaging** is performed\* to exclude other reversible conditions (e.g. Subdural haematoma, normal pressure hydrocephalus) and help provide information on aetiology to guide prognosis and management.

Neuroimaging is required to diagnose dementia

## **Alzheimer's disease (AD)**

Alzheimer's disease is a **progressive degenerative disease of the brain** accounting for the majority of dementia seen in the UK.

Alzheimer's disease is characterised **early** in the disease by **short term memory loss**.

Genetics:

- Most cases are sporadic
- 5% of cases are inherited as an **autosomal dominant** trait.
- Mutations in the amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1) genes are thought to cause the inherited form.
- Apoprotein E allele E4 - encodes a cholesterol transport protein.

Pathological changes:

- 1) Macroscopic = widespread cerebral atrophy, particularly involving the cortex and hippocampus.
- 2) Microscopic = intraneuronal neurofibrillary tangles, neuronal plaques, deficiency of neurons.
- 3) Biochemical = deposition of type A-Beta-amyloid protein in cortex, deficit of Ach from damage to an ascending forebrain projection.

Neurofibrillary tangles:

- Paired helical filaments are partly made from a protein called tau
- In AD tau proteins are excessively phosphorylated

Management:

- 1) NICE now recommend the **three acetyl cholinesterase inhibitors (↑Ach): (Donepezil (Aricept®), Rivastigmine (Exelon®) and (Galantamine)** as options for managing mild to moderate Alzheimer's disease.
- 2) **Memantine (Namenda®):** (a NMDA receptor antagonist) is reserved for patients with moderate - severe Alzheimer's.

Donepezil → SE: **Insomnia, Bradycardia, Heart block and UB obstruction**

The NICE guidelines recommend discontinuation of cholinesterase inhibitors as Donepezil once the mini mental state examination has fallen below 12/30 and possibly consider Memantine, which is licensed for use in moderate to severe dementia.

So pt. **with Dementia on Donepezil (Aricept®)**, then ↓ **MMSE >>> so withdraw Donepezil and consider Memantine.**

### Lewy body dementia (LBD)

Lewy body dementia is an increasingly recognised cause of dementia, accounting for up to **20%** of cases.

It is a **mixture** of Alzheimer's disease with Parkinson's disease.

The characteristic pathological feature is alpha-synuclein **cytoplasmic inclusions (Lewy bodies)** in the substantia nigra, paralimbic and neocortical areas.

The relationship between Parkinson's disease and Lewy body dementia is **complicated**, particularly as dementia is often seen in Parkinson's disease.

Also, **up to 40% of patients with Alzheimer's have Lewy bodies.**

**Neuroleptics** should be **avoided** in Lewy body dementia as patients are extremely sensitive and may develop irreversible Parkinsonism.

Questions may give a history of a patient who has deteriorated following the introduction of an antipsychotic agent (like haloperidol).

EX: A 64-year-old man who is under investigation for parkinsonian symptoms is brought to the GP by his wife. She is concerned her husband is becoming increasingly agitated. The GP prescribes haloperidol. One week later the parkinsonian symptoms have deteriorated markedly. What is the most likely underlying diagnosis? >>> Lewy body dementia.

Features:

- 1) **Progressive cognitive impairment.**
- 2) **Parkinsonism.**
- 3) **Hallucinations** (**visual** or non-visual hallucinations, other features such as delusions may also be seen).
- 4) **Symptoms worsen with neuroleptics/ antipsychotic agent.**

Diagnosis:

- Usually **clinical**.
- **Single-photon emission computed tomography (SPECT)** is increasingly used. It is currently commercially known as a **DaTscan (dopamine transporter scan)**.
  - Dopaminergic iodine-123-radiolabelled 2-carbomethoxy-3-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (123-I FP-CIT) is used as the radioisotope.
  - The sensitivity of SPECT in diagnosing Lewy body dementia is around 90% with a specificity of 100%.
  - Its main drawback is expense.

The findings on conventional imaging such as MRI are generally non-specific.

Lewy body dementia has no specific identifying features on CT or MRI.

### **Normal pressure hydrocephalus**

It is a reversible cause of dementia seen in elderly patients.

It is thought to be secondary to reduced CSF absorption at the arachnoid villi.

These changes may be secondary to head injury, subarachnoid haemorrhage or meningitis.

A **classical triad** of features is seen:

- 1) **Dementia** and bradyphrenia
- 2) **Urinary incontinence**
- 3) **Gait abnormality** (may be similar to Parkinson's disease)

Urinary incontinence + gait abnormality + dementia = normal pressure hydrocephalus.
---

Imaging: **Hydrocephalus** with an **enlarged fourth ventricle**.

Management: **VPS** (Ventriculo-peritoneal shunting).

### Creutzfeldt –Jakob Disease (CJD)

- **Rapidly progressive**, severe invariably **fatal** usually within few months.
- **Dementia**
- **Cerebellar ataxia**.
- Diffuse **myoclonic jerks**: it is typical and progressive, even during the later stage when the patient is stuporous or comatose.
- Ataxia and involuntary movements (for example, myoclonus) usually appear at an interval of about **6 months after the initial symptoms**.
- In the majority of the cases the first symptoms are **psychiatric** (depression, irritability) and **painful sensory symptoms in the LLs**.
- **New variant CJD** usually presents in a young person, in their twenties or thirties.
- EEG is usually normal in new variant CJD.
- **Rapid cognitive decline** in a **young** person with **myoclonus** is strongly suggestive of Creutzfeldt-Jakob disease (CJD).

Investigations:

- **EEG**: characteristic diffuse non-specific slowing **periodic high amplitude sharp wave complexes PSCs** of 1-2 Hz, but diagnosis relies on either specialized tests for prion protein in CSF or **brain biopsy**.
- **MRI**: **Pulvinar sign** > 90% (**bilateral posterior thalamic nuclei high signal abnormalities**) **pathological** in **variant CJD** (not sporadic).
- **CSF**: 14-3-3 protein
- **Prion protein** in tonsils.

### **Sporadic CJD:**

- It is a prion disease.

- Normal prion proteins are found on cell surfaces all over the body mainly in an alpha helix structure.
- Predominantly affects late **mid** aged individuals with mean age of death in the **late 60s**.
- **Memory impairment** and subsequently **rapidly progressive dementia** from few weeks duration to less than 2 years.
- Commonly accompanying features include **cerebellar ataxia**, **pyramidal** and **extrapyramidal signs** and **myoclonus** which are common early features.
- A definitive diagnosis can only be made post-mortem.
- The median duration of illness is 4 months and about 65% of cases die within 6 months.

**EX:** Male pt. 60 years with increasing forgetfulness over the last 3 months, he become more agitated and police brought him home after seeing him wondering in the street, O/E: he has broad based gait, intention tremor, past pointing, myoclonic jerk, brisk reflexes and bilateral up-going plantars >>> **Sporadic CJD**.

### Meningitis: CSF analysis

#### Normal CSF:

Opening pressure	5-18 <b>cm H<sub>2</sub>O</b> (60-150 mm)
Glucose	3.3-4.4 mmol (> <b>2/3 blood glucose</b> )
Protein	0.15-0.45 g/l
WBC	< 5/ <b>mm<sup>3</sup></b>

The characteristic cerebrospinal fluid (CSF) findings in meningitis:

	<b>Bacterial</b>	<b>Viral</b>	<b>Tuberculous</b>
<b>Appearance</b>	Cloudy	Clear/cloudy	Fibrin web
<b>Glucose</b>	Low (< 1/2 plasma)	Normal*	Low (< 1/2 plasma)
<b>Protein</b>	High (> 1 g/l)	Normal/raised	High (> 1 g/l)
<b>White cells</b>	10 - 5,000 polymorphs/mm <sup>3</sup>	15 - 1,000 <b>lymphocytes</b> /mm <sup>3</sup>	10 - 1,000 <b>lymphocytes</b> /mm <sup>3</sup>

The following conditions are associated with **raised lymphocytes**:

- 1) **Viral** meningitis/encephalitis
- 2) **TB** meningitis
- 3) **Partially** treated **bacterial** meningitis
- 4) **SLE**
- 5) Behcet's
- 6) Leukaemia
- 7) Lymphoma
- 8) Lyme disease

The following conditions are associated with **raised protein levels**:

- 1) **Bacterial, Tuberculous, Fungal** meningitis
- 2) **Viral** encephalitis
- 3) **GBS** (Guillain-Barre syndrome)
- 4) **Spinal block** (Froin's syndrome): It describes an increase in CSF protein below a spinal canal blockage (e.g. tumour, disc, infection).

The Ziehl-Neelsen stain is only 20% sensitive in the detection of tuberculous meningitis and therefore **PCR** is sometimes used (sensitivity = 75%).

\*Mumps is unusual in being associated with a low glucose level in a proportion of cases. A low glucose may also be seen in herpes encephalitis

### Post-lumbar puncture headache

Headache following lumbar puncture (LP) occurs in approximately **one-third** of patients. The pathophysiology of is unclear but may relate to a 'leak' of CSF following dural puncture.

It is more common in **young females** with a low body mass index.

Typical features:

- 1) Usually develops **within 24-48 hours following LP** but may occur **up to one week later**.
- 2) **May last several days**.
- 3) **Worsens with upright position**.
- 4) **Improves with recumbent position**.

Factors which may contribute to ↑↑↑headache	Factors which do not contribute to headache
Increased needle size Direction of bevel Not replacing the stylet Increased number of LP attempts	Increased volume of CSF removed Bed rest following procedure Increased fluid intake post procedure Opening pressure of CSF Position of patient

Management:

- **Supportive** initially (analgesia, rest).
- If pain continues for more than 72 hours then specific treatment is indicated, to prevent subdural haematoma.
- TTT options include: **blood patch**, epidural saline and caffeine I.V.

### Herpes simplex encephalitis (HSE)

Herpes simplex (HSV) encephalitis is a very common topic in the exam.

The virus characteristically affects the **temporal** lobes - questions may give the result of imaging or describe temporal lobe signs e.g. aphasia.

Features:

- Fever, headache, vomiting.
- Psychiatric symptoms, change in personality, odd behaviour, becoming aggressive over trivial things, confusion, seizures.
- Focal features e.g. aphasia.
- Peripheral lesions (e.g. cold sores) have no relation to presence of HSV encephalitis.

Pathophysiology:

- HSV-1 responsible for 95% of cases in adults
- Typically affects temporal and inferior frontal lobes

Investigations:

- CSF: lymphocytosis, elevated protein
- **PCR for HSV** (the quickest method).

- CT/ MRI (**MRI** is better): **medial temporal** and **inferior frontal** changes (e.g. **petechial haemorrhages**), low attenuation areas with surrounding oedema - normal in one-third of patients.
- **EEG: lateralised periodic discharges at 2 Hz (BUT is not diagnostic).**

TTT: **I.V Acyclovir** (10-15 mg/kg IV every 8 hrs for **10-14 days**).

The **prognosis** is dependent on whether **acyclovir** is commenced **early**. If treatment is started promptly the mortality is 10-20%.

Left untreated the mortality approaches 80%.

**EX:** A 34-year-old woman who presents with confusion, headache and fever is admitted to the ER. Shortly after admission she has a seizure. A MRI scan is performed which shows patchy haemorrhagic changes in the temporal lobe. Given the likely diagnosis, what is the treatment of choice? **I.V Acyclovir**

### HIV: Neurocomplications

HIV Neuro complications	
Generalised	Focal
1) Encephalitis	1) Toxoplasmosis
2) Cryptococcus	2) Lymphoma
3) PML	3) TB
4) AIDS dementia complex	

### Generalised neurological disease:

#### 1) Encephalitis

- May be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: **oedematous brain**

#### 2) Cryptococcus:

- Most common **fungal** infection of CNS: Cryptococcus neoformans.
- Headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit.



- Meningitis is typical presentation but may occasionally cause a space occupying lesion
- CSF: **high opening pressure, India ink test positive.**
- CT: **meningeal enhancement, cerebral oedema**

### **3) Progressive multifocal leukoencephalopathy (PML):**

- **Widespread demyelination.**
- Due to infection of oligodendrocytes by human **papovirus JC virus** (a polyoma **DNA** virus).
- Symptoms, subacute onset: behavioural changes, speech, motor, visual impairment, ataxia, Head tremor, Focal neurology progressing over a period of months to paresis and even coma.
- Diagnosed by **CSF PCR** for the **JC virus**.
- **CT**: single or multiple lesions, no mass effect, don't usually enhance. **Several areas of Low attenuation diffusely.**
- **MRI** is better - **high-signal demyelinating white matter** lesions are seen.

### **4) AIDS dementia complex:**

- Caused by HIV virus itself
- Symptoms: behavioural changes, motor impairment
- CT: **cortical and subcortical atrophy**

### **Focal neurological lesions:**

#### **1) Toxoplasmosis:**

- Accounts for around **50%** of **cerebral lesions** in patients with **HIV**.
- Constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple **ring enhancing** lesions, mass effect may be seen
- Management: sulfadiazine and pyrimethamine

#### **2) Primary CNS lymphoma:**

- Accounts for around **30%** of cerebral lesions
- Associated with the **Epstein-Barr virus**
- CT: single or multiple **homogenous** enhancing lesions

- Treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours.

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients.

It is clearly important given the vastly different treatment strategies.

Toxoplasmosis	Lymphoma
<b>Multiple</b> lesions Ring or nodular <b>enhancement</b> Thallium SPECT <b>negative</b>	Single lesion Solid (homogenous) enhancement Thallium SPECT positive

### 3) Tuberculosis:

- Much less common than toxoplasmosis or primary CNS lymphoma.
- CT: single enhancing lesion.

### **Head injury: NICE guidance**

NICE has strict and clear guidance regarding which adult patients are safe to discharge and which need further CT head imaging.

The former group are also divided into two further cohorts, those who require an immediate CT head and those requiring CT head within 8 hours of injury:

#### **CT head immediately:**

- 1) GCS < 13 on initial assessment.
- 2) GCS < 15 at 2 hours post-injury.
- 3) Suspected open or depressed skull fracture.
- 4) Any sign of basal skull fracture (haemotympanum, 'panda' eyes, and CSF leakage from the ear or nose, Battle's sign).
- 5) Post-traumatic seizure.
- 6) Focal neurological deficit.
- 7) More than 1 episode of vomiting

**CT head scan within 8 hours of the head injury:**

For adults with any of the following risk factors who have experienced some loss of consciousness or amnesia since the injury:

- 1) Age 65 years or older.
- 2) Any history of bleeding or clotting disorders.
- 3) Dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle or a fall from a height of greater than 1 metre or 5 stairs).
- 4) More than 30 minutes' retrograde amnesia of events immediately before the head injury.

**N.B:** If a patient is on **warfarin** who have sustained a head injury with no other indications for a CT head, **perform a CT head scan within 8 hours** of the injury.

**Head injury: types of traumatic brain injury**

Basics:

- Primary brain injury may be focal (contusion/haematoma) or diffuse (diffuse axonal injury).
- Diffuse axonal injury occurs as a result of mechanical shearing following deceleration, causing disruption and tearing of axons.
- Intra-cranial haematomas can be extradural, subdural or intra-cerebral, while contusions may occur adjacent to (coup) or contralateral (contre-coup) to the side of impact.
- Secondary brain injury occurs when cerebral oedema, ischaemia, infection, tonsillar or tentorial herniation exacerbates the original injury.
- The **normal cerebral auto regulatory** processes are disrupted following trauma rendering the brain more susceptible to blood flow changes and hypoxia.
- The **Cushings reflex (hypertension and bradycardia)** often occurs late and is usually a pre terminal event.

Type of injury	Notes
<b>Extradural (epidural) haematoma</b>	<p>Bleeding <b>into the space between</b> the dura mater and the skull.</p> <p>Often results from <b>acceleration-deceleration trauma</b> or a <b>blow to the side of the head</b>.</p> <p>The majority of extradural haematomas occur in the <b>temporal</b> region where skull fractures cause a rupture of the <b>middle meningeal artery</b>.</p> <p>Features:</p> <ul style="list-style-type: none"> <li>• Features of <b>raised intracranial pressure</b>.</li> <li>• Some patients may exhibit a <b>lucid interval</b>.</li> <li>• A history of a closed head injury, followed by a lucid period followed by decreasing level of consciousness.</li> </ul>
<b>Subdural haematoma (SDH)</b>	<p>Bleeding <b>into the outermost meningeal layer</b>.</p> <p>Most commonly occur around the frontal and parietal lobes.</p> <p>Risk factors include <b>old age</b>, <b>alcoholism</b> and <b>anticoagulation</b>.</p> <p>Slower onset of symptoms than an epidural haematoma.</p> <p><b>Fluctuating</b> confusion/consciousness &gt;&gt;&gt; <b>SDH</b>.</p>
<b>Subarachnoid haemorrhage (SAH)</b>	<p>Usually occurs <b>spontaneously</b> in the context of a ruptured cerebral aneurysm but may be seen in <b>association</b> with other injuries when a patient has sustained a traumatic brain injury.</p>

**EX:** A 14-year-old boy bangs heads with an opponent during an unofficial football game. He is knocked out for 30 seconds and is amnesic for the event. He recovers quickly and continues playing.

Two hours later he complains of headache, begins vomiting then loses consciousness >>> **Extra-Dural haematoma >>> CT brain**.

### Subdural haemorrhage (SDH)

Basics:

- Most commonly secondary to **trauma** e.g. **old person/alcohol falling** over.
- Initial injury may be minor and is often forgotten.
- Caused by bleeding from damaged bridging veins between cortex and venous sinuses.

Features:

- **Classically fluctuating conscious level** (episodes of confusion and between these episodes the pt. is apparently his/her normal self).

**Old patient with Fluctuating consciousness** = subdural haemorrhage (SDH)

Treatment: Neurosurgical review >>>? Burr hole.

### Subarachnoid haemorrhage (SAH)

Causes:

- 1) **85%** are due to **rupture of berry aneurysms**: (conditions associated with berry aneurysms include adult polycystic kidney disease, Ehlers-Danlos syndrome and coarctation of the aorta).
- 2) AV malformations.
- 3) Trauma.
- 4) Tumours.

Investigations:

- 1) **CT**: negative in 5%.
- 2) **LP**: done **after 12 hrs** (for allowing time for **xanthochromia** to develop).
- 3) **Cerebral angiography.**

**Posterior communicating artery aneurysms** can compress the **third** cranial nerve. If the aneurysm ruptures it can cause the **classic** picture of an **ipsilateral painful third nerve palsy**, with the **eye down and out**, **ptosis**, and **pupil dilation**.

Anterior communicating artery aneurysms do not compress the third nerve.

Complications:

- 1) Rebleeding (in 30%).
- 2) Obstructive hydrocephalus (due to blood in ventricles).
- 3) Vasospasm leading to cerebral ischaemia.

Management:

- 1) **Nimodipine** (e.g. **60mg / 4 hr**, if BP allows) has been shown to reduce the severity of neurological deficits but doesn't reduce rebleeding. (The way Nimodipine works in SAH is not fully understood. It has been previously postulated that it reduces cerebral vasospasm hence maintaining cerebral perfusion but this has not been demonstrated in studies).
- 2) Neurosurgical opinion: no clear evidence over early surgical intervention against delayed intervention.

**N.B: Intra-cranial haemorrhage** can cause changes in the **ECG** which are typically **deep symmetrical T-wave inversion** and **prolonged QT interval**.

### Acute confusional state (Delirium)

Acute confusional state is also known as delirium or acute organic brain syndrome.

It affects up to **30%** of **elderly** patients **admitted** to hospital.

Features - wide variety of presentations:

- Memory disturbances (loss of short term > long term)
- May be **very agitated** or withdrawn
- Disorientation
- Mood change
- Visual hallucinations
- Disturbed sleep cycle
- Poor attention

Management:

- Treatment of underlying **cause**
- **Modification of environment**

- The 2006 Royal College of Physicians publication 'the prevention, diagnosis and management of delirium in older people: concise guidelines' recommended **haloperidol 0.5 mg** as the first-line sedative.
- The 2010 NICE delirium guidelines advocate the use of **haloperidol** or **olanzapine**.

N.B: Whilst many doctors may use oral lorazepam in this situation the Royal College of Physicians recommend haloperidol as the first-line sedative.

### Myasthenia gravis (MG)

Myasthenia gravis is an acquired humoral autoimmune disorder resulting in insufficient functioning **acetylcholine receptors**.

**Acetylcholine Receptors Auto Antibodies (ACHRAB)** are seen in **90%** of cases (antibodies are less commonly seen in disease limited to the ocular muscles). These antibodies block Ach receptors at the **post-synaptic** neuromuscular junction.

It is well known to be associated **with other autoimmune diseases** such as **pernicious** anaemia, **thyroid** disease and **rheumatoid arthritis**.

Myasthenia is more common in women (2:1).

It is a neuromuscular disease leading to **fluctuating** muscle weakness & fatigability.

The key feature is **muscle fatigability** - muscles become **progressively** weaker during periods of activity **later in the day** after prolonged use of specific muscle and slowly improve after periods of rest:

- 1) Proximal muscle **weakness**: face, neck, limb girdle.
- 2) Extra ocular muscle weakness: **diplopia** and **Ptosis**.
- 3) **Dysphagia** (worse with liquids than solids).
- 4) **Dysarthria**, slurred speech.

Associations:

- 1) Thymomas in 15%
- 2) Thymic hyperplasia in 50-70%
- 3) Autoimmune disorders: Autoimmune thyroid disorders, RA, SLE, pernicious anaemia.

30-40% of Thymoma cases have coexistent myasthenia gravis.

Thymoma has equal sex distribution and rarely presents < age of 20 years.

Exacerbating factors:

The most common exacerbating factor is exertion resulting in fatigability, which is the hallmark feature of MG. Symptoms become more marked during the day.

The following **drugs** may **exacerbate** myasthenia:

- 1) Penicillamine
- 2) Procainamide
- 3) Quinidine
- 4) Beta-blockers
- 5) Lithium
- 6) Phenytoin
- 7) Gentamicin

Investigations:

- 1) **Tensilon test: IV Edrophonium** reduces muscle weakness temporarily and is sometimes used in the diagnosis of myasthenia gravis (Diagnostic and therapeutic test).
- 2) **Single fibre electromyography (EMG)** is the most **sensitive** test for myasthenia gravis.
- 3) CT thorax to exclude thymoma.
- 4) **CPK normal.**
- 5) Muscle fatigability can be demonstrated at the **bedside** by asking the patient to **count aloud from 1 to 20 slowly** - often inducing slurred speech.
- 6) Fatigable ptosis can be demonstrated by asking the patient to maintain upward gaze without blinking for 30-60 seconds.

Management:

- 1) Long-acting **anticholinesterase** e.g. Pyridostigmine.
- 2) Immunosuppression: prednisolone initially.
- 3) **Thymectomy**: is significantly improve symptoms of myasthenia, and is the next logical step once diagnosis of myasthenia is confirmed.

Management of myasthenic crisis:

- 1) **IVIG** (Intravenous immunoglobulins)
- 2) **Plasmapheresis**



Opinions vary as to whether Plasmapheresis or IVIG should be given as a first-line. Plasmapheresis usually works quicker but involves more expensive equipment.

**Mechanical** dysphagia (for example, oesophageal and gastric carcinoma, oesophageal stricture, etc.) causes dysphagia that is worse with **solids** than liquids. Nasal regurgitation and dysarthria are **not** usually accompanying features of mechanical dysphagia.

**Neurogenic** dysphagia that is worse with **liquids** than solids also associated with dysarthria, nasal regurgitation, coughing and choking episodes during meals.

**Achalasia** typically affects **solids** more than liquids, or **both solids and liquids equally**. It typically presents at earlier age (25 to 40-years-old). Chest pain is a predominant feature, with no weight loss.

**NB: Ocular myasthenia:** **bilateral ptosis** and **variable diplopia**, without proptosis or injection of the eyes, with **normal all pupils reflexes**.

### **Lambert-Eaton Myasthenic Syndrome (LEMS)**

It is seen in **50 %** of cases associated with **small cell lung cancer (SCLC)**, and to a lesser extent breast and ovarian cancer.

It is a rare **paraneoplastic** phenomenon which can precede radiological evidence of the tumour by up to 5 years.

It may also occur independently as an autoimmune disorder.

It is caused by an **antibody** directed **against pre-synaptic** voltage gated **calcium channel (VGCC)** in the **peripheral** nervous system leading to failure of acetyl choline release.

Features:

- 1) **Repeated muscle contractions** after a few minutes will lead to **increased muscle strength** and **return of absent reflexes** (in contrast to myasthenia gravis). (In reality this is seen in only 50% of patients and following prolonged muscle use muscle strength will eventually decrease).
- 2) **Limb girdle (proximal muscle) weakness** (affects lower limbs first).
- 3) **Hypo-reflexia to areflexia** (but normalise with repetitive muscle contraction).
- 4) **Autonomic symptoms: dry mouth, impotence**, difficulty micturating.
- 5) **No bulbar or extraocular muscle involvement** like ophthalmoplegia and ptosis (unlike in myasthenia gravis).

- 6) **No** wasting or fasciculations.
- 7) **No** Sensory affection.

Diagnosis:

- **EMG**: **Incremental** response to **repetitive** electrical stimulation.

- **Anti-VGCC auto Antibodies**: are found in **95%** of cases.

Management:

- 1) Treatment of underlying cancer.
- 2) Immunosuppression, for example with prednisolone ± azathioprine.
- 3) **3,4-diaminopyridine IV** is currently being trialled (works by blocking potassium channel efflux in the nerve terminal so that the action potential duration is increased. Calcium channels can then be open for a longer time and allow greater acetylcholine release to the stimulate muscle at the end plate).
- 4) **IVIG therapy** and **plasma exchange** may be beneficial.

Comparison between Myasthenia gravis (**MG**) & Lambert-Eaton Myasthenic Syndrome (**LEMS**):

	<b>MG</b>	<b>LEMS</b>
Muscle strength	↓ during ongoing exercise	Delayed maximum contraction
Ocular muscle affection	<b>Yes</b>	<b>NO</b>
ANS affection	<b>NO</b>	<b>Yes</b>
Tendon reflexes	Normal	↓ with post-tetanic facilitation
Single nerve stimulation (Amplitude)	Normal	Reduced
Repetitive stimulation	↓ at 3-Hz stimulation	Additional ↑ at 20-Hz stimulation
Ach Receptor Ab	<b>Positive</b>	-----
VGCC Ab	-----	<b>Positive</b>

**Eaton** (1905-1958) U.S. neurologist at Mayo Clinic. **Lambert** (1915-2003) U.S neuro-physiologist at Mayo Clinic and Prof. of physiology at University of Minnesota.

### Narcolepsy

It is excessive daytime somnolence and an overwhelming desire to sleep.

Symptoms include excessive daytime sleepiness (EDS), involuntary sleep episodes, cataplexy (70%), sleep paralysis hallucinations – hypnagogic (at the onset of sleep) and hypnopompic (on awaking).

### Cataplexy

Cataplexy describes the **sudden and transient loss of muscular tone** caused by **strong emotion** (e.g. laughter, being frightened).

Around two-thirds of patients with narcolepsy have cataplexy.

Features range from buckling knees to collapse.

### Neuroleptic malignant syndrome (NMS)

It is a **rare** but **dangerous** condition seen in patients taking **antipsychotic** medication (e.g. Olanzapine haloperidol, chlorpromazine and Citalopram).

It carries a mortality of up to 10% and can also occur with **atypical antipsychotics**.

It may also occur with **dopaminergic drugs (such as levodopa)** for **Parkinson's** disease, usually when the **drug is suddenly stopped** or **the dose reduced**.

It is thought to arise from blockage of dopamine receptors or decrease in availability of dopamine (↓ **Dopamine**).

Primary diagnostic features are altered conscious level, autonomic instability and muscular rigidity with raised CPK

The syndrome can occur **within hours** of initiating drug therapy, but typically takes about **1 week**.

The mortality is between 10-20%.

Features:

- More common in **young male** patients
- **Onset** usually in **first 10 days of treatment** or **after increasing dose of antipsychotic**.

- **Pyrexia**
- **Altered mental status**
- **Muscle rigidity** (sometimes with dysphagia and dysarthria).
- **Extrapyramidal signs, tremors, catatonia, muteness.**
- **Tachycardia**
- **Autonomic dysfunction.**
- A raised **CPK & AST** is present in most cases.
- A **leucocytosis** may also be seen.
- **Renal failure** may occur secondary to rhabdomyolysis
- **Metabolic acidosis.**
- **DIC.**

Management:

- **Stop** antipsychotic.
- **IV fluids** to prevent renal failure.
- **Dopamine agonist: Bromocriptine or Levodopa.**
- **Dantrolene IV** was formerly recommended as monotherapy, case series suggests that when it is used in the absence of Bromocriptine, mortality may actually be increased.

**Dantrolene** is thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum.

EX: A 35-year-old man with a history of schizophrenia is brought to the ED by worried friends due to drowsiness. On examination he is generally rigid. >>> A diagnosis of neuroleptic malignant syndrome should be suspected.

### Epilepsy: classification

Basics:

- Two main categories are **generalised** and **partial** seizures
- Partial seizures may progress to general seizures
- Other types: myoclonic, atypical absence, atonic and tonic seizures are usually seen in childhood

**Generalised** - no focal features, consciousness lost immediately:

- 1) Grand mal (tonic-clonic)
- 2) Petit mal (absence seizures)
- 3) Myoclonic jerks: brief, rapid muscle jerks
- 4) Partial seizures progressing to generalised seizures
- 5) Infantile spasms

**Partial** - focal features depending on location:

- 1) Simple (no disturbance of consciousness or awareness)
- 2) Complex (consciousness is disturbed)
- 3) Simple partial followed by impaired consciousness, or consciousness impaired at onset
- 4) Partial seizures with secondary generalisation
- 5) Temporal lobe → aura, déjà vu, jamais vu; motor → Jacksonian

With simple partial seizures there is no disturbance of consciousness or awareness. Lip smacking is an example of an automatism- an automatic, repetitive act.

### Absence seizures (petit mal)

It is a form of generalised epilepsy that is mostly seen in children.

The typical age of onset of **3-10 years old** and **girls** are affected twice as commonly as boys.

Features: طفلة بتسرح كذا مرة في اليوم لثواني وترجع تاني طبيعية ولا تتذكر ذلك

- 1) Absences last a **few seconds** and are associated with a **quick recovery**.
- 2) Seizures may be provoked by **hyperventilation** or **stress**.
- 3) The child is usually **unaware** of the seizure.
- 4) They may occur **many times a day**.
- 5) EEG: bilateral, symmetrical 3Hz spike and wave pattern.

Management:

- Sodium valproate and ethosuximide are first-line treatment
- **Good prognosis** - **90-95%** become **seizure free in adolescence**.

**N.B:** Carbamazepine may actually exacerbate absence seizure.

**NB:** **Gelastic seizures** should be suspected in cases of **erratic laughing** or **crying**. It can be hard to identify in **young children** but there is usually associated automatisms such as fidgeting or lip smacking or change in sensorium.

### Myoclonic epilepsy:

**Juvenile myoclonic epilepsy** is the **commonest** of the **idiopathic** generalised epilepsies.

**Precipitating factors** include alcohol, menstruation and sleep deprivation.

The condition is genetically linked to the **short arm of chromosome 6**.

Prognosis is extremely favourable if the condition is treated correctly, with many patients becoming seizure-free.

TTT options include: **sodium valproate**, lamotrigine and topiramate.

**Lifelong drug treatment is usually necessary** to avoid relapses in patients who achieve seizure-free status on medication.

### Epilepsy: treatment

Most neurologists now start antiepileptic drugs (**AED**) following a **second** epileptic seizure.

NICE guidelines suggest starting antiepileptic after the **first** seizure **if any** of the following are present: **(4)**:

- 1) The patient has a neurological deficit.
- 2) Brain imaging shows a structural abnormality.
- 3) EEG shows unequivocal epileptic activity.
- 4) The patient or their family consider the risk of having a further seizure unacceptable.

**Monotherapy** should be attempted before combination therapy is started.

A study of patients with previously untreated epilepsy demonstrated that **47%** achieved control of seizures with the use of their **first single** drug.

**14%** became seizure-free during treatment with a **second or third drug**.

An additional **3%** became seizure-free with the use of **two drugs simultaneously**.

**Sodium valproate** is considered the first line treatment for patients with **generalised** seizures with **carbamazepine** used for **partial** seizures.

Epilepsy medication: first-line:

- **Generalised** seizure: **Sodium valproate**
- **Partial** seizure: **Carbamazepine**

**Generalised tonic-clonic seizures:**

- 1) **Sodium valproate**
- 2) Second line: **Lamotrigine** (Lamictal®), Carbamazepine

**Absence seizures (Petit mal):**

- **Sodium valproate** or **Ethosuximide**
- Sodium valproate particularly effective if co-existent tonic-clonic seizures in primary generalised epilepsy.

**Myoclonic seizures:**

- 1) **Sodium valproate**
- 2) Second line: Lamotrigine, clonazepam

**Partial seizures:**

- **Carbamazepine**
- Second line: **lamotrigine\*\***, sodium valproate
- Gabapentin (Neurontin®)

**Phenytoin (Epanutin ®)**

Phenytoin is used to in the management of seizures.

**Mechanism of action:**

**Na channel blocker**, decreasing the sodium influx into neurons which in turn decreases excitability.

**Adverse effects:**

Phenytoin is associated with a large number of adverse effects.

These may be divided into acute, chronic, idiosyncratic and teratogenic.

**1) Acute:**

- Initially: **Cerebellum syndrome**: **Ataxia**, Dizziness, Diplopia, Nystagmus, Chorea, Slurred speech.
- Later: confusion, seizures.

Phenytoin toxicity typically gives rise to a cerebellar-like syndrome

**2) Chronic:**

- Common: **gingival hyperplasia** (secondary to increased expression of platelet derived growth factor, PDGF), **hirsutism** (شعر), **acne**, **coarsening of facial features**, drowsiness.
- Megaloblastic anaemia** (secondary to altered **Folate** metabolism).
- Pancytopenia**
- Peripheral neuropathy**.
- Enhanced vitamin D metabolism causing **osteomalacia**.
- Lymphadenopathy, Pseudolymphoma or, rarely, malignant lymphoma and mycosis-fungoides-like lesions.**

R/ Epanutin + Folic acid + Vit B complex + Pregabalin+ Calcium with Vit D

**3) Idiosyncratic:**

- Fever
- Rashes**, up to severe reactions as toxic epidermal necrolysis (**TEN**)
- Hepatitis
- Dupuytren's contracture (although not listed in the BNF).
- Aplastic anaemia
- Drug-induced lupus

**4) Teratogenic:**

- Associated with cleft palate and congenital heart disease.



**Usage of phenytoin in renal impairment:**

Patient with renal failure, a state in which **drugs** that are usually **highly protein bound**, such as phenytoin, sodium valproate and warfarin. **Lose some of their affinity for protein binding**. This results in **increased availability of free drug** at any given dose, which then **increases the risk of toxicity**.

**So you will find signs of phenytoin toxicity but with normal Phenytoin levels in blood by the lab**

Because **laboratory** assays for phenytoin usually measure **total** drug concentration, this gives a degree of **false reassurance**.

So in patients with renal failure, **dose reduction of phenytoin** is required.

**Sodium valproate (Depakin®):**

It is used in the management of epilepsy and is first line therapy for generalised seizures. It works by **increasing** ↑ **GABA activity**.

Adverse effects:

- 1) GIT: anorexia, nausea, vomiting
- 2) **PCOS like picture**: weight gain, acne, hair loss: so ↓ use in **females**.
- 3) Highly **teratogenic**: neural tube defects.
- 4) **Alopecia صلع (in 12 % of cases)**: regrowth may be curly
- 5) Ataxia
- 6) **Tremor**
- 7) **Hepatitis**
- 8) **Pancreatitis**
- 9) Thrombocytopenia
- 10) Hyponatraemia
- 11) Enzyme **Inhibitor** P450 enzyme system

**Na valproate** SE: nausea, ↑ appetite, ↑ weight gain, **Alopecia (صلع)**, Ataxia, Hepatitis, Pancreatitis and Teratogenic.

Sodium valproate can occasionally have an **idiosyncratic** response leading to **severe** or even **fatal hepatic toxicity**.

**Vigabatrin (Sabril 500 mg tab):**

- 40% of patients develop **visual field defects (constriction of visual fields)**, which may be irreversible.
- Visual fields should be checked every 6 months.
- Other side effect: alopecia.

**N.B:** The 2007 SANAD study indicated that lamotrigine may be a more suitable first-line drug for partial seizures although this has yet to work its way through to guidelines.

**NB:** **Lamotrigine** is associated with **skin rash** (and **Stevens-Johnson syndrome** in severe cases).

**N.B:** **Monotherapy** with another drug should be attempted before combination therapy is started. Caution should be exercised when **combining sodium valproate and lamotrigine** as serious skin rashes such as **Steven-Johnson's syndrome** may be provoked.

**N.B:** Regarding the stopping of anti-epileptic drugs (AED): the 2004 NICE guidelines recommends that can be considered **if seizure free for > 2 years**, with **AEDs being stopped over 2-3 months**. Benzodiazepines should be withdrawn over a longer period.

In patient who has been seizure free for more than 2 years, the chance for recurrence in the next 2 years is 43% if they stop therapy compared with 10% if drugs are continued. Factors that have been shown to increase the risk of re-seizures include:

- Older age.
- History of tonic clonic or myoclonic seizure.
- Previous abnormal brain imaging or EEG.
- Use of multiple AEDs.
- Seizure while on therapy.

**Infantile Spasm (west syndrome):**

- It occurs between 3-12 months of age, managed by **Vigabatrin**.
- It is a **triad** of:
  - 1) Infantile spasm.
  - 2) A pathognomonic EEG pattern (called hypsarrhythmia).
  - 3) Mental retardation.
- International definition requires only **2** out of these 3 elements.

**Carbamazepine:** dose-dependent unwanted side effects: diplopia, nystagmus, ataxia, hyponatremia, hepatotoxicity, Toxic Epidermal Necrolysis (TEN) and rarely BM depression.

### Epilepsy: pregnancy and breast feeding

The risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the foetus, so **her drug should be continued**.

There is **no point in switching therapies** as this could **precipitate** seizures in an otherwise stable patient.

All women thinking about becoming pregnant should be advised to take **folic acid 5 mg per day well before pregnancy to minimise the risk of neural tube defects**.

Around 1-2% of newborns born to non-epileptic mothers have congenital defects. This rises to 3-4% if the mother takes antiepileptic medication.

Other points:

- Aim for **monotherapy**.
- There is **no** indication to **monitor** antiepileptic drug (AED) levels.
- Phenytoin: associated with cleft palate.
- Sodium valproate: associated with neural tube defects.
- Similarly both phenytoin and valproate are associated with teratogenic effects.
- Levetiracetam: insufficient data to its use in pregnancy.
- Topiramate: is associated with major congenital malformation (MCM).
- **Carbamazepine**: often considered the **least** teratogenic of the older antiepileptic.
- In pregnancy total plasma concentrations of anticonvulsants fall, so the **dose** of Carbamazepine **may** need to be **increased**.
- The potential teratogenic effects (particularly **neural tube defects**) of **carbamazepine** do need to be **explained** and in an effort to reduce this risk she should receive **folate** supplements.
- **Screening with alpha fetoprotein (AFP) and 2nd trimester ultrasound** are required.
- **Lamotrigine**: studies to date suggest the rate of congenital malformations may be low. The dose of lamotrigine may need to be increased in pregnancy.

- Lowest rate of MCM were seen for **Carbamazepine** and **Lamotrigine**.
- It is advised that pregnant women taking phenytoin are given vitamin K in the last month of pregnancy to prevent clotting disorders in the newborn.
- **Vitamin K** should be given to the mother **prior to delivery**.

The BNF states '**breast-feeding** is acceptable and generally considered **safe** for mothers with **all antiepileptic drugs**, taken in normal doses, with the possible exception of barbiturates'.

**Breast feeding is acceptable with nearly all anti-epileptic drugs.**

### Neurofibromatosis (NF)

There are two types of neurofibromatosis, NF1 and NF2.

Both are inherited in an **autosomal dominant** fashion.

NF1 is also known as von Recklinghausen's syndrome. It is caused by a gene mutation on **chromosome 17** which encodes neurofibromin and affects around 1 in 4,000.

NF2 is caused by gene mutation on **chromosome 22** and affects around 1 in 100,000.

#### Features:

NF1	NF2
<ul style="list-style-type: none"> <li>➤ <b>Café-au-lait spots</b> (<math>\geq 6</math> to 15 mm in diameter)</li> <li>➤ <b>Axillary/groin freckles</b></li> <li>➤ <b>Iris: <u>Lisch nodules</u></b> in <math>\geq 90\%</math></li> <li>➤ <b>Optic glioma</b></li> <li>➤ <b>Scoliosis</b></li> <li>➤ <b>Pheochromocytomas</b></li> <li>➤ Peripheral neurofibromas</li> <li>➤ A family history in only 50%</li> </ul>	<p>Bilateral acoustic neuromas</p>

- **NF1:** chromosome **17** - as neurofibromatosis has 17 characters.
- **NF2:** chromosome **22** - all the 2's
- **Lisch nodules** in **iris** are seen in **more than 90%**.

Patients with neurofibromatosis may develop **hypertension** for 3 main reasons:

- 1) Coexistent essential hypertension
- 2) Renal vascular stenosis secondary to fibromuscular dysplasia
- 3) Pheochromocytomas

EX: Pt. with HTN and has large cafe-au-lait spots on his trunk and some axillary freckling (i.e. neurofibromatosis), so you should:

- 1) Check renal function to check diagnosis of renal vascular disease.
- 2) Check 24 hr. urinary collection of catecholamines to check Pheochromocytomas.

### Tuberous sclerosis (TS)

It is a genetic condition of **autosomal dominant** inheritance.

The responsible defects having been identified on both **chromosome 9 & 16**.

These chromosomes carry codes for hamartin and tuberin, protein gene products which are responsible for regulation of cell growth.

Like neurofibromatosis, the majority of features seen in TS are **neuro-cutaneous**. Cutaneous features:

- 1) **Depigmented 'ash-leaf' spots** which fluoresce under UV light.
- 2) **Shagreen patches:** roughened patches of skin over lumbar spine.
- 3) **Adenoma sebaceum:** butterfly distribution over nose.
- 4) **Fibromata beneath nails** (subungual fibromata).
- 5) **Café-au-lait spots** may be seen (of course are more commonly associated with neurofibromatosis).

Neurological features:

- 1) **Developmental delay**
- 2) **Intellectual impairment**
- 3) **Epilepsy** (infantile spasms or partial)

Also:

- **Retinal hamartomas**: dense white areas on retina (phakomata)
- Rhabdomyomas of the heart
- Gliomatous changes can occur in the brain lesions
- **Polycystic** kidneys, **renal angiomyolipomata**

**Cigarettes and coffee with a rough stupid person with a butterfly on his nose while he is dancing.**

Cigarettes (ash) – coffee (Café-au-lait spots) – stupid (Developmental and Intellectual) – dancing (epilepsy).

### Essential tremor

Essential tremor (previously called benign essential tremor) is an **AD autosomal dominant** condition which usually affects both upper limbs.

Features:

- **Postural tremor: worse if arms outstretched** (usually 6-8 Hz).
- It is **worse** on **movement** and during **stress**.
- **Improved by alcohol and rest**
- Most common cause of **titubation (head tremor)**

Management:

- **Propranolol** is first-line
- **Primidone** (anticonvulsant) is sometimes used (as in case which cannot give propranolol like in bronchial asthma).

**NB:** **Anxiety** and **drugs** (for example, **salbutamol**, **sodium valproate**, **theophylline**, and **amiodarone**) are commonly associated with limbs tremor.

### Idiopathic intracranial hypertension (IIH)

Idiopathic intracranial hypertension (also known as **pseudo tumour cerebri** and formerly **Benign Intracranial Hypertension (BIH)**) is a condition classically seen in **young, overweight females**.

Its exact cause is **unknown**, but it is most common in overweight young women.

IIH is thought to be due to **impaired CSF absorption** across the arachnoid villi into the dural sinuses.

It is characterised by **raised intracranial pressure** with **normal** CSF cell count and protein content, normal ventricular size, anatomy and position.

**If left untreated** it can result in **permanent visual loss**.

The symptoms classically reported with raised intracranial pressure are frontal headaches, worst when lying flat, coughing, bending, and on waking as well as nausea and vomiting. Patients may also complain of a whooshing sound in their ears, and pain/ numbness or tingling in their arms and legs. Visual symptoms include transient, bilateral episodes of blurred vision, transient visual field defects and double vision.

Features:

- 1) **Headache**
- 2) **Blurred vision**
- 3) **Fundus: Papilledema** with **reduced/absent retinal venous pulsation**
- 4) **Enlarged blind spot**
- 5) **Sudden loss of vision** (If the optic nerve becomes compressed).
- 6) **6<sup>th</sup> nerve palsy** may be present >> **diplopia**
- 7) Reflexes are **preserved** and plantars are flexor. Extensor plantars suggest an alternative diagnosis.
- 8) **Normal** ventricles on CT and MRI
- 9) **CSF opening pressure:** mild increase (more than 20 CmH<sub>2</sub>O).

Obese, young female with headaches, blurred vision and Papilledema, ± OCP (Dianette in PCO) but otherwise normal neurology >>> think idiopathic intracranial hypertension (IIH)

Risk factors:

- **Obesity**
- **Female sex**
- **Pregnancy**
- **Drugs:**
  - 1) **Oral contraceptive pill**,

- 2) Steroids,
- 3) Tetracycline (Doxycycline for acne),
- 4) Nitrofurantoin,
- 5) Vitamin A toxicity

Management:

- Weight loss.
- Diuretics e.g. **acetazolamide**
- **Repeated lumbar puncture or Lumbo-peritoneal (LP) shunt.**
- Surgery: **optic nerve sheath decompression and fenestration** may be needed to prevent damage to the optic nerve.

NB: **Visual loss** is the single threatening complication of idiopathic intracranial hypertension (IIH).

NB: If intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic.

**EX:** A 27-year-old woman is reviewed due to sudden loss of vision in her left eye. She is known to have severe RA and is treated currently with methotrexate, infliximab and prednisolone. She has in the past also used sulfasalazine and hydroxychloroquine. For the past 6 weeks she has developed troublesome headaches. Examination demonstrates bilateral papilledema. Which one of the following is most likely to be responsible for this presentation? >> **Intracranial hypertension** probably **secondary to prednisolone**. Patients may lose sight suddenly if the optic nerve becomes compressed.

#### Migraine: diagnostic criteria

The International Headache Society has produced the following diagnostic criteria for migraine without aura:



Point	Criteria
<b>A</b>	At least 5 attacks fulfilling criteria B-D
<b>B</b>	Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated)
<b>C</b>	Headache has at least two of the following characteristics: <ol style="list-style-type: none"> <li>1) <b>Unilateral</b> location*</li> <li>2) <b>Pulsating</b> quality (i.e., varying with the heartbeat).</li> <li>3) <b>Moderate or severe</b> pain intensity.</li> <li>4) <b>Aggravation by or causing avoidance of</b> routine physical activity (e.g., walking or climbing stairs).</li> </ol>
<b>D</b>	During headache at least one of the following: <ol style="list-style-type: none"> <li>1) <b>Nausea</b> and/or <b>vomiting</b>*</li> <li>2) <b>Photophobia</b> and <b>phonophobia</b> (occurs in around 75% of patients).</li> </ol>
<b>E</b>	Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not occur for the first time in close temporal relation to the other disorder)

\*In children, attacks may be shorter-lasting, headache is more commonly bilateral, and gastrointestinal disturbance is more prominent.

**N.B: Migraine with aura** (around **1 in 3 migraine patients**) tends to be easier to diagnose with a typical aura being progressive in nature and may occur hours prior to the headache. Typical aura include a transient hemianopic disturbance or a spreading scintillating scotoma ('jagged crescent'). Sensory symptoms may also occur.

**NB: A complicated migraine** is one which results in **hemi** sensory or **hemi** motor findings associated with a typical migraine presentation i.e. **it is like TIA but** the patient is **young** age and has **past medical history for migraines**.

### Migraine: management

It should be noted that as a general rule **5-HT receptor agonists** are used in the acute treatment of migraine whilst **5-HT receptor antagonists** are used in prophylaxis.

**ACute** → 5HT1 **AG**onist

Prophylaxis → 5HT2 antagonist &  $\beta$ B

Migraine:

- **Acute**: (Triptan + NSAID) **or** (Triptan + paracetamol).
- **Prophylaxis**: Topiramate (Topamax®) or propranolol.

Acute treatment:

- First-line: offer combination therapy with an **oral triptan** and an **NSAID**, or an oral triptan and paracetamol.
- For young people aged 12-17 years consider a **nasal triptan** in preference to an oral triptan.
- If the above measures are not effective or not tolerated offer a non-oral preparation of metoclopramide or prochlorperazine and consider adding a non-oral NSAID or triptan

Prophylaxis:

- Prophylaxis should be given **if** patients are **experiencing  $\geq 2$  attacks per month**. Modern treatment is effective in about 60% of patients.
- NICE advice either **Topiramate (Topamax®)** or **Propranolol 80 – 240 mg OD** according to the person's preference, comorbidities and risk of adverse events'.
- Propranolol should be used in preference to topiramate in women of child bearing age as it may be teratogenic and it can reduce the effectiveness of hormonal contraceptives.
- If these measures fail NICE recommend 'a course of up to 10 sessions of **acupuncture** over 5-8 weeks' or **gabapentin**.
- NICE recommend: 'Advise people with migraine that **riboflavin** (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people'

- For women with predictable menstrual migraine treatment NICE recommend either frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) as a type of 'mini-prophylaxis'.
- **5-HT<sub>2</sub> antagonists** like:
  - “**Pizotifen**” is **no** longer recommend. Adverse effects such as weight gain & drowsiness are common.
  - “**Methysergide**” is very **rarely** used as associated with retroperitoneal fibrosis.

**Avoid aspirin** in children < 16 years as risk of Reye's syndrome

**Codeine** would also be a **poor** choice as it has **limited benefit in migraine**.

Patients with **migraine** experience **delayed gastric emptying** during **acute attacks**. So **decrease effect of analgesics**. For this reason analgesics are often combined **prokinetic** agents such as metoclopramide.

**Topiramate side effects:**

- **Renal stones**
- **Weight loss**
- **Cognitive impairment**
- **Tingling** in extremities.

**Triptans**

Triptans are specific **5-HT<sub>1B/1D</sub> receptors agonists** used in the acute treatment of migraine.

They are generally used first-line in combination therapy with an NSAID or paracetamol.

Prescribing points:

- Should be taken **as soon as possible after the onset of headache, rather than at onset of aura.**
- Oral, dispersible, nasal spray and subcutaneous injections are available.

Adverse effects:

- '**Triptan sensations**' - tingling, heat, throat tightness and chest tightness, heaviness, pressure.

Contraindications:

- Patients with a history of, or significant risk factors for, **IHD** or cerebrovascular disease.

### Migraine: pregnancy, contraception and other hormonal factors

Migraine during pregnancy:

- **Paracetamol** 1g is first-line
- **Aspirin** 300mg or **ibuprofen** 400mg can be used second-line in the first and second trimester.

Migraine and menstruation:

- Many women find that the frequency and severity of migraines increase around the time of menstruation.
- SIGN recommends that women are treated with **mefenamic acid** or a combination of **aspirin**, **paracetamol** and **caffeine**.
- **Triptans** are also recommended in the acute situation, NICE recommend either frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) as a type of 'mini-prophylaxis'.

Migraine and the combined oral contraceptive (COC) pill:

- If patients have migraine with aura then the COC is **absolutely contraindicated** due to an **increased risk of stroke** (relative risk 8.72).
- Ergot derived compounds and triptans are contraindicated for the ttt of **hemiplegic migraine** because of the risk of precipitating a stroke.

Migraine and hormone replacement therapy (HRT):

- Safe to prescribe HRT for patients with a history of migraine but it may make migraines **worse**.

### Cluster headache (CH)

Cluster headaches are more common in **men** (10:1) and **smokers**.

Features:

- Pain typical occurs **once or twice a day, each episode lasting 15 mins - 2 hours**.
- Clusters typically last 4-12 weeks.
- **Intense pain around one eye** (recurrent attacks '**always**' affect **same** side).

- Accompanied by **eye redness, lacrimation, lid swelling**
- **Miosis** and **ptosis** in a minority.
- **Nasal** stuffiness, **Rhinorrhoea**.
- Patient is **restless during an attack**
- Examination between the attacks should be normal.

Episodic eye pain, lacrimation, nasal stuffiness occurring daily >>> cluster headache

Management:

- **Acute:** **100% oxygen**, **SC Sumatriptan**, nasal lidocaine.
- **Prophylaxis:** **Verapamil**, prednisolone.
- Consider specialist referral

**NB:** **Sumatriptan** has been associated with **chest pain** in up to 17% of cases, possibly due to **vasospasm**. Also it is associated with **MI** and so **contraindicated** in people with known **IHD**.

**D.D:** **Chronic paroxysmal hemicrania (CPH)** has features of cluster headaches but is associated with attacks of **shorter duration** and **increased frequency** e.g. each headache can last between **3-45 minutes** and occur **20-40 times per day**. It responds very well to **indomethacin**.

**N.B:** Some neurologists use the term **trigeminal autonomic cephalgia** to group a number of conditions including cluster headache (CH), chronic paroxysmal hemicrania (CPH) and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT).

### Pituitary apoplexy

**Sudden** enlargement of pituitary tumour **secondary** to haemorrhage or infarction. A pituitary adenoma usually pre-exists.

Endocrinologically, the main initial problem is a **lack of adrenocorticotrophic hormone (ACTH)**, which results in a lack of cortisol and the features of an '**Addisonian crisis**', i.e. hypotension, hyponatraemia, hyperkalaemia and hypoglycaemia. Subacutely, there can be deficiency in thyroid stimulating hormone (TSH) and gonadotropins (LH and FSH).

Features:

- 1) **Sudden onset headache** similar to that seen in SAH.
- 2) **Vomiting**
- 3) **Neck stiffness**
- 4) **Visual field defects:** classically bitemporal superior quadrantic defect.
- 5) **Extra ocular** nerve palsies in up to 80%, with **III** nerve palsy the commonest finding.
- 6) Features of pituitary insufficiency e.g. **Hypotension** secondary to **hypoadrenalism.**

**MRT pituitary** to confirm the diagnosis

TTT: **Hydrocortisone IV** should be given to prevent Addisonian crisis.

**EX:** A 47-year-old man presents to the Emergency Department with a 3 day history of severe headache associated with vomiting. There is no past medical history of note. On examination blood pressure is 98/62 mmHg, pulse is 108 bpm and temperature is 37.0°C. There is mild neck stiffness and a partial third nerve palsy of the left eye. Blood tests reveal: Na<sup>+</sup> = 130, K= 5.2, Low free T4. The most likely diagnosis is >> Pituitary apoplexy.

### **Medication overuse headache**

It is one of the most common causes of chronic daily headache.

It may affect up to 1 in 50 people.

Features:

- **Present for ≥ 15 days per month.**
- Developed or worsened **whilst taking regular** symptomatic medication.
- Patients using opioids and Triptans are at most risk.
- May be psychiatric co-morbidity.

Management (SIGN guidelines):

- Simple analgesics and Triptans should be **withdrawn abruptly** (may initially worsen headaches).
- Opioid analgesics should be **gradually withdrawn.**

Medication overuse headache:

- Simple analgesia + Triptans: **stop abruptly**
- Opioid analgesia: **withdraw gradually**

### Acoustic neuroma

Acoustic neuromas (more correctly called **vestibular schwannomas**: it is a **benign** primary intracranial tumour of the **myelin forming cells** of the vestibulocochlear nerve CN **VIII**).

It accounts for approximately 5% of intracranial tumours and **90 % of cerebellopontine angle**.

The term “acoustic” is a misnomer as the tumour rarely arises from the acoustic (or cochlear) division of the vestibulocochlear nerve.

Features can be predicted by the affected cranial nerves:

- Cranial nerve (5) V: **absent corneal reflex**
- Cranial nerve (7) VII: facial palsy
- Cranial nerve (8) VIII: hearing loss, vertigo, tinnitus

Bilateral acoustic neuromas are seen in neurofibromatosis type 2.

**MRI of the cerebellopontine angle** is the investigation of choice.

It is a **benign** neoplasm and the lesion can be **resected** with a **good prognosis**

Loss of corneal reflex → think of Acoustic neuroma

### Benign paroxysmal positional vertigo (BPPV)

It is one of the most common causes of vertigo encountered.

It is characterised by the sudden onset of dizziness and vertigo triggered by **changes in head position**.

The average age of onset is 55 years and it is less common in younger patients. Features:

- Vertigo triggered by change in head position (e.g. rolling over in bed or gazing upwards).

- May be associated with nausea.
- Each episode typically lasts 10-20 seconds.
- **Positive Dix-Hallpike manoeuvre.**

BPPV has a good prognosis and usually resolves spontaneously after a few weeks to months. Symptomatic relief may be gained by:

- **Epley manoeuvre** (successful in around 80% of cases)
- Teaching the patient exercises they can do themselves at home, for example Brandt-Daroff exercises.
- Medication is often prescribed e.g. Betahistine (Betaserc ®) but it tends to be of limited value.

### **Meniere's disease**

It is a disorder of the **inner ear** of **unknown** cause.

It is characterised by excessive pressure and progressive dilation of the endolymphatic system.

It is more common in **middle-aged adults** but may be seen at any age.

Meniere's disease has a **similar** prevalence in **both men and women**.

Features:

- **Recurrent** episodes of **vertigo**, tinnitus and hearing loss (**sensorineural**, i.e. **+ve Weber's test**).
- Vertigo is usually the prominent symptom.
- A sensation of **aural fullness** or **pressure** is now recognised as being common.
- Other features include **nystagmus** and a positive Romberg test
- Episodes last minutes to hours.
- Typically symptoms are unilateral but bilateral symptoms may develop after a number of years.

Natural history:

- Symptoms **resolve** in the **majority** of patients **after 5-10 years**
- Some patients may be left with hearing loss.
- Psychological distress is common.



## Management:

- ENT assessment is required to confirm the diagnosis.
- Patients should inform the DVLA. The current advice is to cease driving until satisfactory control of symptoms is achieved.
- Acute attacks:
  - Buccal or intramuscular **Prochlorperazine**.
  - Admission is sometimes required.
- **Prevention: Betahistine** may be of benefit.

## Tinnitus (causes):

<b>Meniere's disease</b>	Associated with hearing loss, vertigo, tinnitus and sensation of fullness or pressure in one or both ears.
<b>Otosclerosis</b>	Onset is usually at 20-40 years. Conductive deafness. Tinnitus. Normal tympanic membrane. (10% of patients may have a 'flamingo tinge', caused by hyperaemia). Positive family history.
<b>Acoustic neuroma</b>	Hearing loss, vertigo, tinnitus Absent corneal reflex is important sign Associated with neurofibromatosis type 2
<b>Hearing loss</b>	Causes include excessive loud noise and presbycusis
<b>Drugs</b>	<u>Aspirin</u> <u>Aminoglycosides</u> <u>Lasix</u> <u>Quinine</u>
<b>Other causes</b>	Impacted ear wax  Chronic suppurative otitis media (CSOM)

### **Rinne's and Weber's test**

Performing both to allows differentiation of conductive and sensorineural deafness.

#### **Rinne's test:**

- Tuning fork is placed over the mastoid process until the sound is no longer heard, followed by repositioning just over external acoustic meatus.
- Air conduction (AC) is normally better than bone conduction (BC).
- If  $BC > AC$  then conductive deafness.

#### **Weber's test:**

- Tuning fork is placed in the middle of the forehead equidistant from the patient's ears.
- The patient is then asked which side is loudest.
- In unilateral **sensorineural** deafness, **sound** is **localised** to the **unaffected** side.
- In unilateral **conductive** deafness, sound is **localised** to the **affected** side.

<b>EX:</b> Weber's test: If sound is localized to the <u>Rt.</u> side: so either <u>Rt. <b>conductive</b></u> deafness or <u>Lt <b>sensorineural</b></u> deafness.
--

### **Intracranial venous thrombosis**

Overview:

- Can cause cerebral infarction, much less common than arterial causes.
- **50%** of patients have **isolated sagittal sinus thrombosis** - the remainder have coexistent lateral sinus thrombosis and cavernous sinus thrombosis.
- Venous sinus thrombosis is associated with the **oral contraceptive pill**, the **post-partum period** and **other hypercoagulable states**.

Features:

- Headache (may be sudden onset)
- Nausea & vomiting

#### **Sagittal sinus thrombosis:**

- May present with seizures and hemiplegia
- Parasagittal biparietal or bifrontal haemorrhagic infarctions are sometimes seen

**Cavernous sinus thrombosis:**

- 1) Other causes of cavernous sinus syndrome: local infection (e.g. sinusitis), neoplasia, trauma
- 2) **Periorbital oedema.**
- 3) **Ophthalmoplegia:** 6th nerve damage typically occurs before 3rd & 4th.
- 4) **Trigeminal nerve (5th)** involvement may lead to hyperaesthesia of upper face and eye pain.
- 5) **Central retinal vein thrombosis.**

**Lateral sinus thrombosis:**

- 6th and 7th cranial nerve palsies.

**EX:** A 28-year-old female, **3 days post-partum**, develops **severe headache** associated with **seizures**.

During her pregnancy her BP had been mildly elevated in the third trimester.

On examination, she had a GCS of 15 but was slightly **confused** and drowsy. Her temperature was 37.5°C, she had mild nuchal rigidity but neurological examination was otherwise normal.

The most likely diagnosis >>> **Cortical vein thrombosis** >>> Do **MRV**.

TTT is Anti-coagulation

**NB:**

- **Post-partum period** is a risk factor of **cortical vein** and **sinus thrombosis**.
- It typically presents with **headache**, **seizures** and **focal** neurological deficit **2 to 3 weeks postpartum** (but is also seen earlier).
- Although eclampsia would be in the differential diagnosis in this case, **nuchal rigidity** is **not** a typical feature which points more to the direction of cortical vein thrombosis.
- The **eclampsia** seizures can in fact occur antepartum, intrapartum, or postpartum. If a seizure does occur **postpartum**, it usually occurs **within the first 24 hours after delivery**.
- Other clinical presentations include an idiopathic intracranial hypertension (BIH) type of picture (papilledema, visual disturbances and headaches) or a subacute encephalopathic picture. Thrombophilia screen should be performed.

**EX:** A 30-year-old lady presented with **headache** which she first noticed as she was picking up **her 5-week-old baby**. صداع وزغلة من النور لسيدة بعد الولادة

On admission she was **unable to tolerate the lights** and complained of feeling sick. Fundoscopy showed **bilateral papilledema**, and she was complaining that she was unable to see on her left side. **CT head showed a small right occipital bleed >>> venous sinus thrombosis >>> TTT: urgent LMWH.**

This lady has developed a venous sinus thrombosis peri-partum resulting in symptoms of headache, photophobia and vomiting.

The small occipital bleed has resulted from venous congestion and she needs urgent ttt with LMWH to prevent clot propagation and further complications.

This woman's symptoms are not as a result of a subarachnoid aneurysm, so aneurysm coiling and nimodipine are not appropriate.

A lumbar puncture is not appropriate as she does not have idiopathic intracranial hypertension.

She does not have migraine and so a triptan is not appropriate.

### Altitude related disorders

There are **three** main types of altitude related disorders:

- 1) Acute mountain sickness (**AMS**), which may progress to
- 2) High altitude pulmonary oedema (**HAPE**) or
- 3) High altitude cerebral oedema (**HACE**).

All are due to the chronic hypobaric hypoxia which develops at high altitudes.

AMS is generally a self-limiting condition.

Features of AMS start to occur above 2,500 - 3,000m, developing gradually over 6-12 hours and potentially last a number of days:

- Headache
- Nausea
- Fatigue

Prevention and treatment of AMS:

- The risk of AMS may actually be positively correlated to physical fitness.
- Gain altitude at no more than 500 m per day.

- **Acetazolamide** (a carbonic anhydrase inhibitor) is widely used to **prevent** AMS and has a supporting evidence base.
- **Treatment: descent.**

A minority of people above 4,000m go onto develop high altitude pulmonary oedema (HAPE) or high altitude cerebral oedema (HACE), potentially fatal conditions:

- HAPE presents with classical pulmonary oedema features
- HACE presents with headache, ataxia, Papilloedema

Management of HAPE:

- **Descent**
- **Oxygen** if available
- **Nifedipine, Dexamethasone, Acetazolamide**, phosphodiesterase type V inhibitors\*

Management of HACE:

- **Descent**
- **Dexamethasone**

\*The relative merits of these different treatments has only been studied in small trials. All seem to work by reducing systolic pulmonary artery pressure

### **DVLA: neurological disorders**

The guidelines below relate to car/motorcycle use unless specifically stated. For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter.

Specific rules:

- **First seizure: 6 months off driving\*.**
- For patients with **established epilepsy** they must be **fit free for 12 months** before being able to drive.
- **Stroke or TIA: 1 month off** driving
- **Multiple TIAs** over short period of times: **3 months off** driving
- Craniotomy e.g. For meningioma: 1 year off driving\*\*
- Pituitary tumour: craniotomy: 6 months; trans-sphenoidal surgery 'can drive when there is no debarring residual impairment likely to affect safe driving'

- Narcolepsy/cataplexy: cease driving on diagnosis, can restart once 'satisfactory control of symptoms'.
- Chronic neurological disorders e.g. multiple sclerosis, motor neuron disease: DVLA should be informed, complete PK1 form (application for driving licence holder's state of health).

Syncope:

- Simple faint: no restriction
- Single episode, explained and treated: 1 month off
- Single episode, unexplained: 6 months off
- Two or more episodes: 12 months off

\*Previously rule was 12 months. It is now 6 months off driving if the licence holder has undergone assessment by an appropriate specialist and no relevant abnormality has been identified on investigation, for example EEG and brain scan where indicated.

\*\*If the tumour is a benign meningioma and there is no seizure history, licence can be reconsidered 6 months after surgery if remains seizure free.

#### Motor neuron disease (MND): types

MND is a neurological condition of **unknown cause** which can present with **both UMNL and LMNL** signs.

There are a number of clues which point towards a diagnosis of MND:

- 1) **LMN** signs in arms and **UMN** signs in legs
- 2) **Fasciculation**
- 3) **Wasting of the small hand muscles**/tibialis anterior is common.
- 4) **10%** of patients with MND have **dementia** (front temporal) (**FTD**).
- 5) **NO sensory affection** (vague sensory symptoms may occur early in the disease (e.g. limb pain) but 'never' sensory signs).
- 6) **NOT external ocular muscles affection.**
- 7) **NO cerebellar signs.**
- 8) Abdominal reflexes are usually preserved and sphincter dysfunction if present is a late feature.

'Fasciculations' >>> think MND, most commonly Amyotrophic lateral sclerosis.

It **rarely presents before 40 years** and **various 4 patterns** of disease are recognised including: amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy and bulbar palsy.

In some patients however, there is a combination of clinical patterns.

**1) Amyotrophic lateral sclerosis (ALS):**

- The most common type of MND (**50%** of patients).
- Typically **LMN** signs in arms and **UMN** signs in legs.
- In familial cases the gene responsible lies on chromosome 21 and codes for superoxide dismutase.

**2) Primary lateral sclerosis:**

- **UMN** signs only.

**3) Progressive muscular atrophy:**

- **LMN** signs only.
- Affects distal muscles before proximal
- Carries **best prognosis**

**4) Progressive bulbar palsy:**

- Palsy of the tongue, muscles of chewing/swallowing and facial muscles due to loss of function of brainstem motor nuclei.
- Carries **worst prognosis**.

**Diagnosis:**

The diagnosis of motor neuron disease is **clinical**, but nerve conduction studies will show normal motor conduction and can help exclude a neuropathy.

**EMG** (Electromyography) shows a ↓ number of action potentials with a ↑ amplitude.

**MRI** is usually performed to exclude the differential diagnosis of cervical cord compression and myelopathy.

**Management:**

**1) Riluzole (Rilutek®):**

- Prevents stimulation of glutamate receptors (Anti-glutamate).
- Used **mainly in amyotrophic lateral sclerosis**.
- Prolongs life by about 3 months.
- Expensive.

**2) Respiratory care:**

- **NIV** (Non-invasive ventilation, usually BIPAP) is used at night.
- Studies have shown that **NIV has a survival benefit** of around 7 months.

**MND** (Motor neuron disease) >>> **ttt: NIV** is better than Riluzole.

**Prognosis: poor:** 50% of patients die within 3 years.

**Myotonic dystrophy**

Myotonic dystrophy (also called **dystrophia myotonica, DM**) is an **inherited myopathy** with features developing at around **20-30 years old**.

It is the most common adult muscular dystrophy.

It affects **skeletal, cardiac** and **smooth** muscle + **eyes, endocrine, CNS**.

There are 2 main types of myotonic dystrophy, DM1 and DM2.

Genetics:

- **Autosomal dominant**
- A **trinucleotide** repeat disorder
- DM1 is caused by a **CTG** repeat at the end of the DMPK (Dystrophia Myotonica-Protein Kinase) gene on chromosome **19**.
- DM2 is caused by a repeat expansion of ZNF9 gene on chromosome 3.

The key differences are listed in table below:



DM1	DM2
<ul style="list-style-type: none"> <li>- DMPK gene on chromosome 19.</li> <li>- Distal weakness more prominent.</li> </ul>	<ul style="list-style-type: none"> <li>- ZNF9 gene on chromosome 3.</li> <li>- Proximal weakness more prominent.</li> <li>- Severe congenital form not seen.</li> </ul>

General features:

- 1) **Myotonia** (tonic spasm of muscle) (**slow-relaxing grip** may be noticed on initial hand-shake with the patient and is typical of myotonic dystrophy).
- 2) **Myotonic facies** (long, 'haggard' appearance).
- 3) **Atrophy** of temporalis, masseters, facial muscle.
- 4) **Frontal balding**
- 5) **Bilateral ptosis**
- 6) **Neck muscles**, including sternocleidomastoid, are involved early in the course of disease.
- 7) **Cataracts** >> lead to loss of red reflexes of eyes.
- 8) **Dysarthria** (secondary to myotonia of the tongue and pharynx).
- 9) **Dysphagia**

Other features:

- 1) **Reduced reflexes** with myotonia
- 2) Weakness of **arms** and **legs** (**distal** initially)
- 3) **Mild mental / Intellectual impairment**
- 4) **DM**
- 5) **Testicular atrophy**
- 6) **Cardiac involvement: heart block (1 st degree HB a prolonged PR interval is seen in around 20-40% of patients) or (CHB), and cardiomyopathy.**

**Dystrophia myotonica - DM1**

- Autosomal **D**ominant
- **D**istal weakness initially
- **D**iabetes
- **D**ysarthria
- **D**ysphagia

**Diagnosis** can be made on electromyogram (**EMG**) and muscle biopsy.

**EX:** A 29-year-old female with weakness in her arms, leading to increasing difficulties at work. On examination she has a bilateral ptosis and loss of the red-reflex in both eyes. Urine testing also reveals glycosuria. What is the most likely diagnosis? >> **Dystrophia myotonica - DM1.**

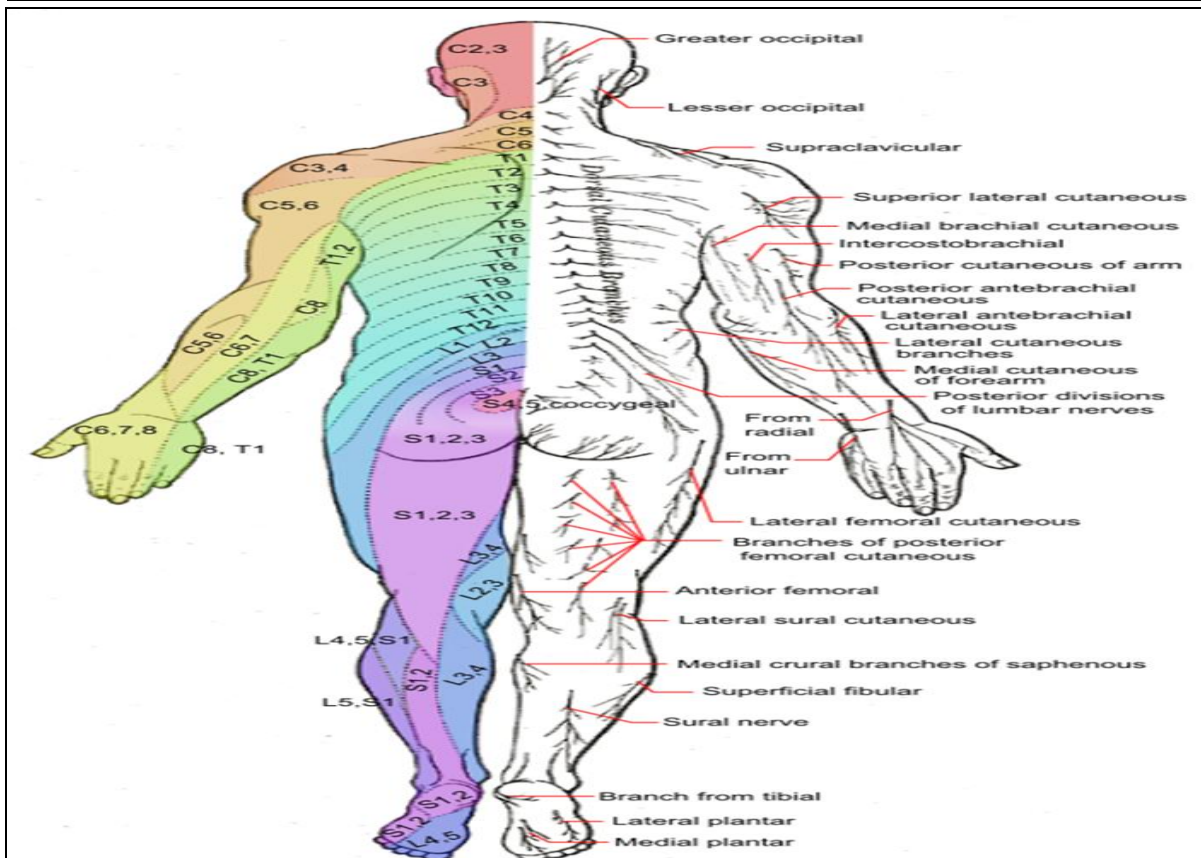
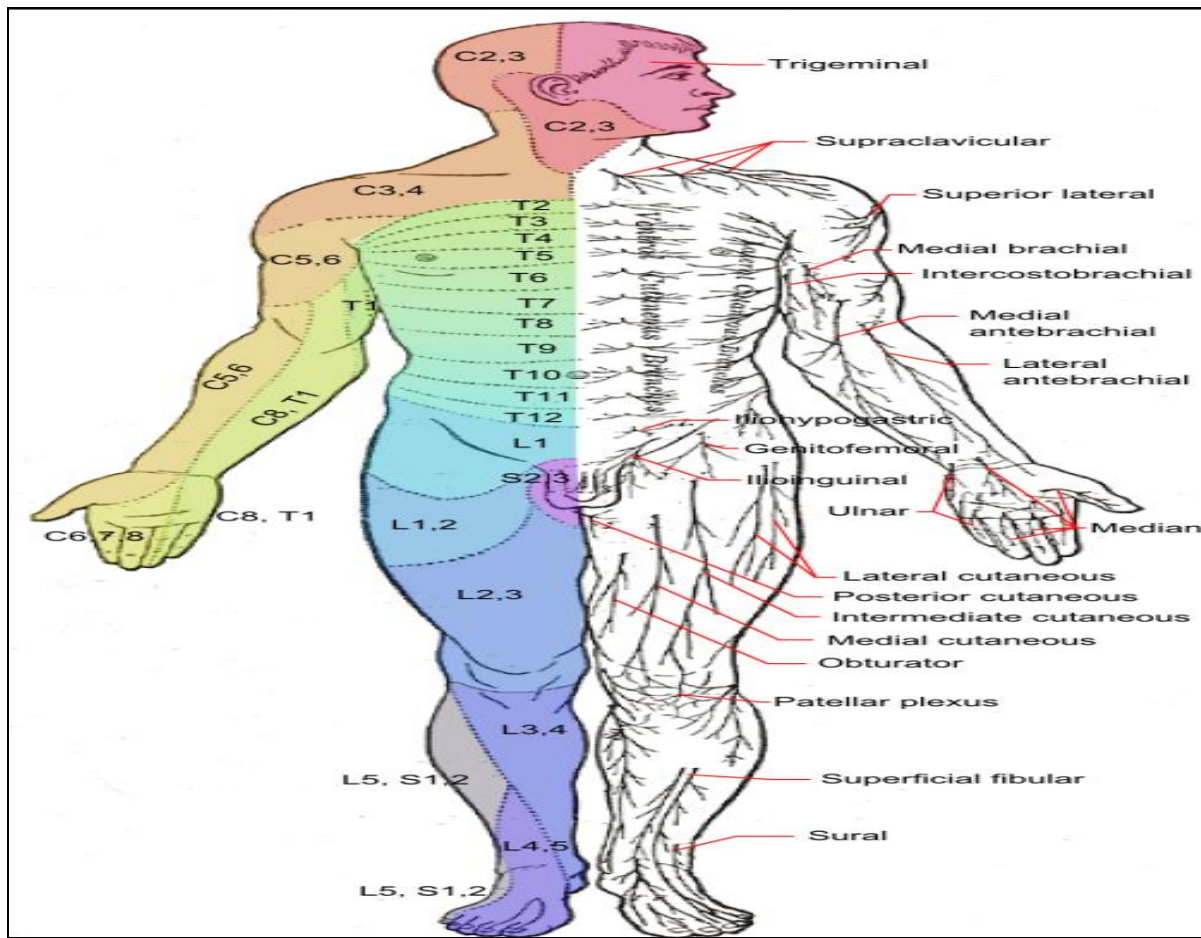
**EX:** A 27-year-old female presents complaining of generalised weakness. Examination of her face reveals bilateral ptosis, dysarthric speech and a slow-relaxing grip. What is the most likely diagnosis? >> **Dystrophia myotonica - DM1.**

**III:**

- Ankle-foot orthosis and splints: for foot drop.
- Lid-lifting surgery has no place as the ptosis is progressive, except in severe cases; also ± cataract extraction.

## Dermatomes

Nerve root	Landmark	Mnemonics
C2	Posterior half of the skull (cap)	
C3	High turtleneck shirt	
C4	Low-collar shirt	
<b>C5, C6</b>	Thumb + index finger	Make a 6 with your L hand by touching the tip of the thumb & index finger together - C6
<b>C7</b>	<b>Middle finger + palm of hand</b>	
C8	Ring + little finger	
<b>T4</b>	<b>Nipples</b>	T4 at the Teat Pore
T5	Inframammary fold	
<b>T7</b>	<b>Xiphoid process</b>	
<b>T10</b>	<b>Umbilicus</b>	BellybuT-TEN
T12	Pubic bone region	
<b>L1</b>	<b>Inguinal ligament</b>	L for ligament, 1 for 1nguinal
<b>L4</b>	<b>Knee caps</b>	Down on aLL fours - L4
<b>L5</b>	<b>Big toe</b> , dorsum of foot (except lateral aspect)	L5 = Largest of the 5 toes
<b>S1</b>	Lateral foot, <b>small toe</b>	S1 = the smallest one
S2, S3	Genitalia	



**Restless legs syndrome (RLS)**

It is a syndrome of **spontaneous, continuous lower limb movements** that may be associated with **paraesthesia**.

It is extremely common, affecting between **2-10%** of the general population.

Males and females are **equally** affected and a **family history** may be present.

Clinical features:

- **Uncontrollable urge to move legs** (akathisia). Symptoms initially occur at **night** but as condition progresses may occur during the day. Symptoms are worse at rest.
- **Paraesthesias** e.g. 'crawling' or 'throbbing' sensations.
- Movements during sleep may be noted by the **partner** - periodic limb movements of sleeps (PLMS).

Causes and associations:

- There is a positive **family history in 50%** of patients with **idiopathic** RLS.
- Iron deficiency anaemia.
- Uraemia
- DM
- Pregnancy

The diagnosis is clinical although **bloods to exclude iron deficiency anaemia may be appropriate (as Ferritin)**.

Management:

- Simple measures: **walking**, stretching, massaging affected limbs.
- Treat any iron deficiency.
- **Dopamine agonists** are first-line treatment (e.g. **Ropinirole**, Pramipexole, and Rotigotine).
- Benzodiazepines.
- Gabapentin.

EX: A 67-year-old woman comes for review with her husband. Her husband complains that she is constantly getting up from bed at night and pacing around the bedroom. She complains of 'antsy' legs and a 'horrible, creeping sensation'. Her

symptoms generally come on in the evening and are only relieved by moving round.  
>>> Restless legs syndrome (RLS) >> ttt: **Ropinirole**.

## **Chorea**

Chorea describes **involuntary, rapid, jerky** movements which often **move** from one part of the body to another.

Chorea is caused by damage to the **basal ganglia**, especially the **caudate nucleus**.

Slower, sinuous movement of the limbs is termed athetosis.

Causes of chorea:

- 1) **Huntington's disease, Wilson's disease, Ataxic telangiectasia.**
- 2) Rheumatic fever: Sydenham's chorea.
- 3) SLE, anti-phospholipid syndrome, vasculitis (PAN, Behcet's disease).
- 4) Drugs: oral contraceptive pill, L-dopa, antipsychotics.
- 5) Pregnancy: chorea gravidarum.
- 6) Thyrotoxicosis.
- 7) Neuro-acanthocytosis.
- 8) Polycythaemia rubra vera.
- 9) **CO poisoning**, cyanide, opiates, mercury.
- 10) Cerebrovascular disease.

**Tetrabenazine** works as a **VMAT-inhibitor** (vesicular monoamine transporter-2), involved in transportation of monoamines. It is indicated for **Huntington's chorea** to reduce hyperkinetic movements.

## **Ataxic telangiectasia**

Basics:

- **Autosomal recessive** disorder
- Combined immunodeficiency disorder

Features:

- 1) **Cerebellar ataxia**
- 2) **Telangiectasia**

3) **Recurrent chest infections**

- 4) 10% risk of developing **malignancy**, lymphoma or leukaemia, but also non-lymphoid tumours

### Hemiballism

Hemiballism occurs following damage to the **subthalamic nucleus**.

Ballistic movements are **involuntary, sudden, jerking, severe flinging** movements **following no particular pattern** which occur **contralateral** to the side of the lesion.

The ballistic movements primarily affect the **proximal limb musculature** whilst the distal muscles may display more choreiform-like movements.

Symptoms may decrease whilst the patient is asleep.

Aetiology:

\* Stroke in elderly, with arteriosclerotic risk factors including HTN, DM, IHD, dyslipidaemia.

\* Infection or inflammatory in young.

Anti-dopaminergic agents (e.g. **Haloperidol**) are the mainstay of treatment.

### Von Hippel-Lindau syndrome (VHL)

VHL syndrome is an **autosomal dominant** condition predisposing to **neoplasia**.

It is due to an **abnormality in the VHL gene** on **short arm of chromosome 3**.

Features

- 1) **Cerebellar haemangiomas** (Ataxia).
- 2) **Retinal haemangiomas**: are bilateral in 25% of patients and may lead to **vitreous haemorrhage**.
- 3) **Renal cysts** (premalignant).
- 4) **Extra-renal cysts**: epididymis, pancreatic, hepatic.
- 5) **Phaeochromocytoma**.
- 6) Endolymphatic sac tumours.

### Friedreich's ataxia

Friedreich's ataxia is the most common of the **early-onset hereditary** ataxias.

It is an **autosomal recessive**, trinucleotide repeat disorder characterised by a GAA repeat in the X25 gene on chromosome 9 (frataxin).

**Neurodegeneration** of cerebellum, Pyramidal tracts and dorsal root ganglia.

So there will be **cerebellum dysfunction**, **spastic paraparesis** and **absent reflexes in lower limbs**.

Friedreich's ataxia is unusual amongst trinucleotide repeat disorders in **not demonstrating the phenomenon of anticipation**.

The typical age of onset is **10-15 years old**.

#### Neurological features:

- 1) Gait ataxia and Kyphoscoliosis ± bilateral pes cavus are the most common presenting features.
- 2) **Cerebellar ataxia** (Dysarthria, Nystagmus).
- 3) **Optic atrophy**
- 4) **Pyramidal weakness:**
- 5) **Extensor plantars response with absent ankle jerks.**
- 6) Sensory-motor neuropathy
- 7) Spinocerebellar tract degeneration

#### Other features:

- 1) **HOCM** Hypertrophic obstructive cardiomyopathy (**90%**, most common cause of death)
- 2) **DM** Diabetes mellitus (10-20%)
- 3) **High-arched palate**



### Wernicke's encephalopathy

Wernicke's encephalopathy is a **neuropsychiatric** disorder caused **by thiamine deficiency** which is most commonly seen in **alcoholics**.

It is caused by lesions in the medial thalamic nuclei, mammillary bodies, periaqueductal and periventricular brainstem nuclei and superior cerebellar vermis.

Rarer causes include: persistent vomiting, stomach cancer, dietary deficiency and after bariatric surgery.

A classic **triad** of **Confusion**, **ataxia** (**nystagmus**), and **Ophthalmoplegia**.

In Wernicke's encephalopathy **petechial haemorrhages** occur in a variety of structures in the brain including the mammillary bodies and ventricle walls.

Features (wide variety of presentations):

- 1) **Confusion**, altered GCS.
- 2) **Nystagmus** (the most common ocular sign).
- 3) **Ataxia**.
- 4) **Ophthalmoplegia**.
- 5) Peripheral sensory neuropathy.
- 6) Impairment of **short** term **memory**.

Investigations:

- 1) Decreased red cell transketolase.
- 2) MRI.

TTT: It is a medical emergency, requiring **urgent IV thiamine 50 mg IV**.

The episode of Wernicke's encephalopathy may be precipitated by **IV dextrose** administration which has exhausted his vitamin B reserves, hence **B vitamins must be administered** to **all alcoholic** patients requiring **dextrose**.

**Alcohol** is a common cause of **hypoglycaemia**, and can be rapidly life-threatening if not recognised. Common initial symptoms are tachycardia and sweating. RBS should be checked in all patients who become acutely unwell.

N.B: Inability to acquire **new memories** with subsequent compensatory **confabulation** تسامر by the patient >>> suggests the development of **Korsakoff's amnesic syndrome**:

Other symptoms may include: Delirium, Anxiety, Fear, Depression, Confusion, Delusions, Insomnia, Painful extremities, sometimes bilateral wrist drop but more frequently bilateral foot drop with pain or pressure over the long nerves.

**Marchiafava Bignami Syndrome**: Corpus callosum degeneration from chronic alcohol excess.

### Multiple Sclerosis (MS)

It is an **UMNL**.

It is also known as **disseminated** sclerosis or encephalomyelitis disseminate.

It is an **autoimmune** disease in which the body's immune system attacks his own **CNS (brain and spinal cord)** leading to **demyelination** of the CNS and hence **UMNL** signs are seen.

Onset usually occurs in **young adults**, more common in **females**.

Patients with multiple sclerosis may present with non-specific features, for example around **75%** of patients have **significant lethargy**.

Remember that **MS** affects the **CNS**, whereas **SCD** subacute combined degeneration of the cord **affects central and peripheral nerves**.

Remember that **MS** is a **central nervous system (CNS)** disorder causing **UMNL findings only**.

NB: Fasciculations are a LMNL finding hence MS cannot be the cause of the patient's fasciculations.

### Subtypes:

**Relapsing-remitting**: characterized by unpredictable relapse followed by periods of months to years of relative quiet (remission) with no new signs of disease activity. Deficits suffered during attacks may either resolve or leave sequelae. This describes **the initial course of 85-90% of individuals with MS**. When deficits always resolve between attacks, it is referred to as benign MS.

**Primary progressive:** about 10-15% of individuals who never have remission after their initial MS symptoms. It is characterized by progression of disability from onset with no or only occasional minor remission and improvements. The age of onset of that type is later than other types.

**Secondary progressive:** those with initial relapsing remission MS who then begin to have progressive neurological decline between acute attacks without any definite periods of remission. The median time between disease onset and conversion from relapsing-remission to secondary progressive type is 19 years.

**Progressive relapsing:** those who from onset have a steady neurologic decline but also suffer clear superimposed attacks. It the least common type.

### **Non-standard behaviours**

#### **Features:**

##### **Visual:**

- 1) Optic neuritis: common presenting feature
- 2) Optic atrophy
- 3) Central scotoma
- 4) **Uhthoff's phenomenon:** worsening of vision following rise in body temperature (e.g. during a hot bath). ضعف النظر بعد دش حمام دافىء
- 5) Internuclear ophthalmoplegia.

##### **Motor:**

- **Spastic weakness:** most commonly in the **legs** (NO HYPOTONIA).
- Patellar clonus
- Positive plantars
- Brisk reflexes

##### **Sensory:**

- 1) Pins/needles
- 2) Numbness
- 3) Trigeminal neuralgia
- 4) **Lhermitte's syndrome:** Paraesthesias in limbs on neck flexion

**Cerebellar:**

- Ataxia: more often seen during an acute relapse than as a presenting symptom
- Tremor

**Others:**

- Urinary incontinence/ retention
- Sexual dysfunction
- Intellectual deterioration

**Diagnosis:**

The gold standard for diagnosis of MS remains clinical assessment, with evidence of **white matter** symptoms and signs **disseminated in time and space**.

**MRI** is the investigation which will show **periventricular white matter plaques** of **different ages** and in **different locations**, to add weight to the clinical assessment.

CT brain will not show these changes.

Diagnosis: (demonstration of lesions disseminated in time and place):

**1) MRI (Brain & Spinal cord):**

- i. High signal T2 lesions.
- ii. Periventricular **plaque**.

**2) CSF:**

- i. **Oligoclonal bands** (not in serum)
- ii. ↑ Intrathecal synthesis of IgG

**3) VEP:**

- i. **Delayed**, but well preserved wave form.

**Treatment in multiple sclerosis:**

It is focused at reducing the frequency and duration of relapses. **There is no cure**.

**Acute relapse:**

High dose steroids (e.g. **IV Methylprednisolone**) may be given **for 3-5 days** to shorten the length of an acute relapse.

It should be noted that steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function).

**Disease modifying drugs:**

**Beta-interferon** has been shown to reduce the relapse rate by up to 30%. Certain criteria have to be met before it is used:

- Relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided.
- Secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided).
- Reduces number of relapses and MRI changes, however doesn't reduce overall disability.

Beta-interferon can reduce the relapse rate by approximately one third for the first 2 years of treatment.

There are 3 products used, beta-interferon 1a (Avonex and Rebif), both of which are licensed for relapsing-remitting MS and beta-interferon 1b (Betaferon), licensed for both relapsing remitting and for secondary progressive forms of MS.

Patient should fulfil the following criteria from the Association of British Neurologists (ABN) for commencing beta-interferon therapy:

- 1) Had more than 2 separate episodes within the last 2 years.
- 2) Is more than 18-years-old, and
- 3) Can walk more than 100 metres.

Contraindications to beta-interferon are:

- 1) History of severe clinical depression
- 2) Uncontrolled epilepsy
- 3) Hepatic dysfunction, and
- 4) Myelosuppression.

**Other drugs** used in the management of multiple sclerosis include:

- **Glatiramer acetate:** immunomodulating drug - acts as an 'immune decoy'.
- **Natalizumab:** a recombinant monoclonal antibody that antagonises Alpha-4 Beta-1-integrin found on the surface of leucocytes, thus inhibiting migration of leucocytes across the endothelium across the blood-brain barrier into parenchymal tissue.
- **Fingolimod:** sphingosine 1-phosphate receptor modulator, it has also been reported to be a cannabinoid receptor antagonist as well as a ceramide synthase inhibitor. It is an immunomodulator, which prevents lymphocytes from leaving lymph nodes. An oral formulation is available.

**Some specific problems:**

Spasticity:

- **Baclofen** and **gabapentin** are first-line.
- Other options include diazepam, Dantrolene and tizanidine.
- Physiotherapy is important
- Cannabis and Botox are undergoing evaluation.
- Hallucinations are occasionally seen on the baclofen withdrawal.

Bladder dysfunction:

- May take the form of urgency, incontinence, overflow etc.
- Guidelines stress the importance of getting an ultrasound first to assess bladder emptying - anticholinergics may worsen symptoms in some patients.
- If significant residual volume → intermittent self-catheterisation.
- If no significant residual volume → anticholinergics may improve urinary frequency.

**Good prognosis features:**

- 1) **Female** sex
- 2) **Young** age of onset
- 3) **Relapsing-remitting** disease
- 4) **Sensory** symptoms
- 5) **Long interval** between first two relapses

Ways of remembering prognostic features that: the **typical** patient carries a **better** prognosis than an atypical presentation.

**Guillain-Barre syndrome (GBS): (Post-infectious polyradiculopathy)**

It is an **immune-mediated acute inflammatory demyelinating polyneuropathy**.

GBS describes an immune mediated **demyelination** of the **peripheral** nervous system often triggered by an **infection** such as **viral** (CMV), viral pneumonia or **bacterial** (classically **Campylobacter jejuni**).

GBS is a **post-infectious acute polyneuritis** typified by **elevated CSF protein** with few cells and often normal glucose.

Pathogenesis:

- Cross reaction of antibodies with gangliosides in the peripheral nervous system.
- Correlation between anti-ganglioside antibody (e.g. anti-GM1) and clinical features has been demonstrated.
- Anti-GM1 antibodies in 25% of patients.

The characteristic features of GBS is **progressive weakness of all four limbs**.

The weakness is classically **ascending** i.e. the **lower extremities** are affected first, however it tends to affect **proximal** muscles earlier than the distal ones.

**Ascending symmetrical progressive weakness and numbness** affecting initially the **legs** and extending to involve the upper limb.

Weakness begins in the legs and progressively ascends to involve the trunk, upper limbs and finally the bulbar muscles (**Landry's ascending paralysis**).

Asymmetry is present in only 9% of patients, with **symmetrical** involvement being **typical**.

Sensory symptoms tend to be mild (e.g. distal paraesthesia, peripheral sensory neuropathy) with **very few sensory signs (NO sensory loss)**.

Usually there is **painless** progression over days or weeks, but in cases of abrupt onset, there may be tenderness or muscle pain.

Some patients experience back pain in the initial stages of the illness.

Other features:

- **Areflexia** (All tendon reflexes were absent and the plantar responses were flexor).
- Cranial nerve involvement e.g. diplopia
- **Autonomic** dysfunction: e.g. **urinary retention** and **postural hypotension & tachycardia**.
- **CSF protein is elevated** to more than **twice** the upper limit of normal, with normal glucose and no pleocytosis. Bacterial cultures are negative and viral cultures rarely isolate anything.
- The **dissociation between a high CSF protein, normal glucose and a lack of CSF cellular response in a person with an acute or subacute polyneuropathy** is **diagnostic** of Guillain-Barre syndrome.

- Although LP is an important part of GBS assessment, a normal CSF protein does not exclude the condition.

Less common findings:

- Papilloedema: thought to be secondary to reduced CSF resorption.

**EX:** A 50-year-old woman with a 2 week history of difficulty walking and weakness in her arms.

O/E, there was **proximal** and distal limb weakness which was more marked in the **legs** than the arms. **All tendon reflexes were absent** and **the plantar responses were flexor**. There was **no sensory loss**.

BP in the supine position was 140/78 mmHg & was 110/70 mmHg on standing.

What is the most likely diagnosis >>> classical presentation of **Guillain-Barre**

**Complications include:**

- **Bulbar** involvement occurs in **50%**, with a risk of aspiration and respiratory insufficiency which can be problematic.
- In **20%** of cases there is **urinary incontinence or retention**.

**Miller Fisher syndrome:**

- It is a variant of Guillain-Barre syndrome (**GBS**)
- Associated with **ophthalmoplegia** and **ataxia**.
- The **eye muscles** are typically affected **first**.
- Usually presents as a **descending** paralysis rather than ascending as seen in other forms of Guillain-Barre syndrome.
- **Anti-GQ1b antibodies** are present in **95%** of cases (highly specific).

**Bickerstaff's encephalitis** is like Miller-Fisher **BUT** there are **drowsiness** and **brisk reflexes**.

**Management:**

- 1) **Plasma exchange**
- 2) **IVIG** (IV immunoglobulins) **0.5 g/kg/day for 5 days**: as effective as plasma exchange. No benefit in combining both treatments. IVIG may be easier to administer and tends to have fewer side-effects.

Steroids and immunosuppressants have not been shown to be beneficial.



**FVC** (Forced **vital capacity**) regularly to **monitor respiratory function**.

FVC is also the best way to monitor respiratory function in any neurological disorders that can affect the respiratory muscles (e.g. GBS, myasthenia gravis) and a better indication of the need for **ventilation**.

**FVC** is used to monitor respiratory function in **GBS**

**Prognosis:**

- 20% suffer permanent disability, 5% die
- **Poor prognostic features**
  - 1) **Age > 40 years**
  - 2) Previous history of a **diarrhoeal** illness (specifically *Campylobacter jejuni*)
  - 3) High **anti-GM1 antibody titre**
  - 4) Poor upper extremity muscle strength
  - 5) Need for ventilatory support
  - 6) There is currently contradictory evidence as to whether a gradual or rapid onset of GBS is associated with a poor outcome.

**Diaphragmatic** weakness occurs in **30%** of patients with patients with GBS and involvement of the neck muscles, tongue and palate leads to further respiratory compromise.

Respiratory muscle function is best monitored by frequent assessment of the forced vital capacity (**FVC**).

**ITU** admission is recommended when **FVC is less than 20 mL/kg** and **intubation** is recommended in most cases when **FVC is less than 15 mL/kg**.

**EX:** A **female** patient aged **30** has a **5 year history** of difficulty getting upstairs and out of a low chair and mild upper limb weakness but no pain. There is no family history. She presented with severe **type 2 respiratory failure**. **EMG** showed evidence of **myopathy**. Which is the most likely diagnosis?

**Acid maltase deficiency** typically presents with **insidious onset** of **proximal myopathy** and **early respiratory muscle weakness**.

**NB: Botulism:** have the same clinical presentation of **descending weakness** (i.e. opposite in direction of GBS) with **autonomic dysfunction** (fixed dilated pupils).

It is a **neuromuscular junction disorder** and therefore nerve conduction studies and EMG are normal.

**Repetitive nerve stimulation shows incremental responses**, is diagnostic of botulism.

**NB: CIDP (Chronic inflammatory demyelinating polyneuropathy)** is clinically similar to GBS (hyporeflexia or areflexia, paraesthesia and mild sensory deficits in the upper and lower extremities, weakness) except that it follows a **chronic progressive course**.

### Meralgia paraesthetica

- Caused by compression of **lateral cutaneous nerve of thigh**.
- Typically burning sensation over antero-lateral aspect of thigh.

Burning thigh pain >>? Meralgia paraesthetica >> lateral cutaneous nerve of thigh compression.

### Neuropathic pain

Neuropathic pain may be defined as pain which arises following damage or disruption of the nervous system.

It is often difficult to treat and responds poorly to standard analgesia.

Examples include:

- 1) Diabetic neuropathy
- 2) Post-herpetic neuralgia
- 3) Trigeminal neuralgia
- 4) Prolapsed intervertebral disc

NICE issued guidance in 2010 on the management of neuropathic pain:

- First-line treatment\*: oral **Amitriptyline** or **Pregabalin**.
- If satisfactory pain reduction is obtained with amitriptyline but the person cannot tolerate the adverse effects (it is better to avoid amitriptyline in pt. with

BPH due to the risk of urinary retention), consider oral imipramine or nortriptyline as an alternative.

- Second-line treatment: if first-line treatment was with amitriptyline, switch to or combine with pregabalin. If first-line treatment was with pregabalin, switch to or combine with amitriptyline.
- Other options: pain management clinic, **tramadol** (no other strong opioids), topical lidocaine for localised pain if patients unable to take oral medication.

\*Please note that for some specific conditions the guidance may vary. For example:

- **Duloxetine** for **diabetic neuropathy**.
- **Carbamazepine** is used first-line for **trigeminal neuralgia**.

### Trigeminal neuralgia

Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain. The vast majority of cases are idiopathic but compression of the trigeminal roots by tumours or vascular problems may occur.

The International Headache Society defines trigeminal neuralgia as:

- A unilateral disorder characterised by brief electric shock-like pains, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve.
- The pain is commonly evoked by light touch, including washing, shaving, smoking, talking, and brushing the teeth (trigger factors), and frequently occurs spontaneously.
- Small areas in the nasolabial fold or chin may be particularly susceptible to the precipitation of pain (trigger areas).
- The pains usually remit for variable periods.

Management:

- **Carbamazepine** is first-line\*
- Failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology.

\*The 2010 NICE neuropathic pain guidelines recommend using amitriptyline or pregabalin first-line for non-diabetic neuropathic pain, but makes no specific recommendation for trigeminal neuralgia.

Due to the amount of evidence supporting carbamazepine in trigeminal neuralgia and its recommendation in consensus guidelines (including Clinical Knowledge Summaries) the author does not feel that this recommendation should be changed for now.

**Peripheral neuropathy (PN): demyelinating vs. axonal**

**Axonal pathology:**

- 1) **Alcohol**
- 2) **DM** ( $\pm$  a demyelinating picture)
- 3) **Vit B12** deficiency ( $\pm$  a demyelinating picture)
- 4) **Vasculitis**
- 5) **Renal failure.**
- 6) HSMN type II

**Demyelinating pathology:**

- 1) **GBS** (Guillain-Barre syndrome)
- 2) **CIDP** (Chronic inflammatory demyelinating polyneuropathy).
- 3) Paraprotein neuropathy
- 4) Amiodarone
- 5) HSMN type I

**Hereditary Sensorimotor Neuropathy (HSMN)**

It is a relatively new term which encompasses **Charcot-Marie-Tooth disease** (also known as **perineal muscular atrophy**).

Over 7 types have been characterised - however only 2 are common clinically:

- HSMN **type I**: primarily due to **demyelinating** pathology
- HSMN **type II**: primarily due to **axonal** pathology

HSMN type I:

- **Autosomal dominant**, so **50%** of children will be affected.
- Due to defect in PMP-22 gene (which codes for myelin).
- Features often start at puberty.
- **Motor** symptoms predominate.
- **Distal muscle wasting, pes cavus (high arched foot), clawed toes.**
- **Foot drop, leg weakness** often **first** features.
- Nerve Conduction Velocity (**NCV**) **< 30 m/sec.**

### Nerve conduction studies (NCS)

It is useful in determining between axonal and demyelinating pathology

Axonal	Demyelinating
<ul style="list-style-type: none"> <li>➤ Normal conduction velocity</li> <li>➤ Reduced amplitude</li> </ul>	<ul style="list-style-type: none"> <li>➤ Reduced conduction velocity</li> <li>➤ Normal amplitude</li> </ul>

	Axonal	Demyelinating
Conduction velocity	Normal	Reduced
Amplitude	Reduced	Normal

### Peripheral neuropathy

It may be divided into conditions which predominately cause a motor or sensory loss.

Predominately <b>motor</b> loss	Predominately <b>sensory</b> loss:
<ul style="list-style-type: none"> <li>• GBS.</li> <li>• CIDP.</li> <li>• HSMN</li> <li>• Porphyria.</li> <li>• Lead poisoning</li> <li>• Diphtheria</li> </ul>	<ul style="list-style-type: none"> <li>• DM.</li> <li>• Alcoholism.</li> <li>• Vit B12 deficiency.</li> <li>• Uraemia.</li> <li>• Amyloidosis.</li> <li>• Leprosy.</li> </ul>

#### Alcoholic neuropathy:

- Secondary to both direct toxic effects and reduced absorption of Vit. B.
- Sensory symptoms typically present prior to motor symptoms.

#### Vitamin B12 deficiency:

- Subacute combined degeneration (SCD) of spinal cord.
- Dorsal column usually affected first (joint position, vibration) prior to distal paraesthesia.

### Drugs causing peripheral neuropathy

Drugs causing a peripheral neuropathy:

- 1) **Antibiotics: Nitrofurantoin, Metronidazole**
- 2) **Amiodarone**
- 3) **Isoniazid**
- 4) **Vincristine** & most chemotherapy
- 5) **TCA** (Tricyclic antidepressants)

### Autonomic neuropathy

Features:

- Impotence,
- Urinary retention.
- Postural hypotension e.g. drop of 30/15 mmHg
- Inability to sweat
- Loss of decrease in heart rate following deep breathing
- Pupils: dilates following adrenaline instillation

Causes:

- **DM**
- **GBS** (Guillain-Barre syndrome)
- **Parkinson's**
- **MSA** (Multisystem atrophy)(Shy-Drager syndrome)
- Infections: **HIV**, Chagas' disease, neurosyphilis
- Drugs: antihypertensives, TCA
- Craniopharyngioma

### Carpal tunnel syndrome

It is caused by compression of median nerve in the carpal tunnel.

History:

- Pain/pins and needles in thumb, index, middle finger
- Unusually the symptoms may 'ascend' proximally
- Classically **at night**
- **Patient shakes his hand to obtain relief.**

Examination:

- **Weakness of thumb abduction** (abductor pollicis brevis)
- **Wasting of thenar eminence** (NOT hypothenar)
- Tinel's sign: Tapping causes paraesthesia
- Phalen's sign: flexion of wrist causes symptoms

The median nerve also supplies **most of the muscles of the thenar eminence**, namely the (**LOAF**):

- 1) **L**ateral two lumbricals
- 2) **O**pponens pollicis
- 3) **A**bductor pollicis brevis, and
- 4) **F**lexor pollicis brevis

NB: The remaining small muscles of the hand are supplied by the ulnar nerve.

Causes:

- Idiopathic
- Pregnancy
- Oedema e.g. heart failure
- Lunate fracture
- Rheumatoid arthritis

Electrophysiology:

- Motor + sensory: prolongation of the action potential

Treatment:

- 1) Corticosteroid injection
- 2) Wrist splints at night
- 3) Surgical decompression (flexor retinaculum division)

**NB:** The **palmar cutaneous branch** of the **median nerve** lies **superficial** to the flexor retinaculum and does **not** pass through the carpal tunnel. It supplies the **skin over the thenar eminence**, which is therefore **spared** in carpal tunnel syndrome.

So Pt. with CTS have preserved skin sensation over thenar area.

### Ulnar nerve

It arises from medial cord of brachial plexus (C8, T1)

The ulnar nerve supplies **all the muscles of the hands except thenar** muscles and the lateral two lumbricals which are supplied by median nerve.

Motor: to

- Medial two lumbricals
- Adductor pollicis >> Adduction of the thumb
- Interossei
- Hypothenar muscles: (opponens digiti minimi, abductor digiti minimi, flexor digiti minimi).
- Flexor carpi ulnaris

Sensory to:

- Medial 1 1/2 fingers (palmar and dorsal aspects)

**Patterns of damage:**

#### **Damage at wrist:**

- **'Claw hand'** - hyperextension of the metacarpophalangeal joints and flexion at the distal and proximal interphalangeal joints of the 4th and 5th digits
- Wasting and paralysis of intrinsic hand muscles (except lateral two lumbricals)
- Wasting and paralysis of **hypothenar muscles**
- **Sensory loss to the medial 1 1/2 fingers** (palmar and dorsal aspects)

#### **Damage at elbow:**

- As above (however, **ulnar paradox** - clawing is more severe in distal lesions)
- Radial deviation of wrist



## Paraneoplastic syndromes affecting nervous system

### 1) Lambert-Eaton Myasthenic syndrome:

- Associated with small cell lung cancer (also breast and ovarian).
- Antibody directed against pre-synaptic voltage gated calcium channel in the peripheral nervous system.
- Can also occur independently as autoimmune disorder.

### 2) Anti-Hu: (imagine **H** sticks as 2 lungs or 2 brain hemispheres)

- Associated with small cell lung carcinoma and neuroblastoma.
- **Sensory neuropathy** - may be **painful**
- Cerebellar syndrome
- Encephalomyelitis

### 3) Anti-Yo: (imagine **Y** as lady's private organs)

- Associated with **ovarian** and **breast** cancer
- **Cerebellar** syndrome

### 4) Anti-GAD antibody:

- Associated with breast, **colorectal** and small cell lung carcinoma
- **Stiff person's syndrome** or **diffuse hypertonia**.

### 5) Anti-Ri:

- Associated with **breast** and small cell lung carcinoma
- **Ocular opsoclonus-myoclonus**

**EX:** A 66-year-old woman is investigated for ascites and found to have ovarian cancer. She presents due to 'unsteadiness'. On examination there is evidence of nystagmus and past-pointing. Which one of the following antibodies is most likely to be present? >>> Anti-Yo.

**EX:** A 65-year-old man who is known to have metastatic colorectal cancer presents for review. Since last been seen he reports being generally stiff and on examination is noted to have diffuse hypertonia. Which antibodies are most likely to be responsible for this presentation? >>> Anti-GAD.

**Mitochondrial diseases**

Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria.

It encodes protein components of the respiratory chain and some special types of RNA.

Mitochondrial inheritance has the following characteristics:

- Inheritance is **only via the maternal line** as the sperm contributes no cytoplasm to the zygote.
- All children of affected males will not inherit the disease
- All children of affected females will inherit it
- Generally encode rare neurological diseases
- Poor genotype: phenotype correlation - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy.

Histology:

- **Muscle biopsy** classically shows 'red, ragged fibres' due to increased number of mitochondria.

Examples include:

- 1) **Leber's optic atrophy**: bilateral painless visual loss in young boy.
- 2) **MELAS** syndrome: **Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like episodes**.
- 3) **MERRF** syndrome: **Myoclonus Epilepsy with Ragged-Red Fibres**.
- 4) **Kearns-Sayre syndrome**: onset in patients < 20 years old, external ophthalmoplegia, retinitis pigmentosa. Bilateral ptosis may be seen.
- 5) **Sensorineural hearing loss**

### **Prescribing in pregnant patients**

Very few drugs are known to be completely safe in pregnancy.

The list below largely comprises of those known to be **harmful**.

Some countries have developed a grading system.

#### **Antibiotics:**

- **Tetracyclines**
- **Aminoglycosides**
- **Sulphonamides** and **trimethoprim**
- **Quinolones:** the BNF advises to avoid due to arthropathy in some animal studies

Other drugs:

- **ACEI** and **ARBs**
- **Statins**
- **Warfarin**
- **Sulfonylureas**
- **Retinoid** (including topical)
- **Cytotoxic** agents

The majority of antiepileptics including valproate, carbamazepine and phenytoin are known to be potentially harmful.

The decision to stop such treatments however is difficult as uncontrolled epilepsy is also a risk

### **Pituitary tumours**

Hormones secreted:

- **Prolactin- 35%**
- No obvious hormone, 'non-functioning', 'chromophobe' - 30%
- Growth hormone - 20%
- Prolactin and growth hormone - 7%
- ACTH - 7%
- Others: TSH, LH, FSH - 1%

NB: **Prolactinomas** are unusual as **medical** therapy is **first** line, **even if visual** field defects are present.

The main indications for surgery are tumours resistant to dopamine agonists.

**Prolactinoma** management >> **Medical** therapy (**dopamine agonist**) is almost always **first-line**, even if visual field defects are present.

### Transient global amnesia (TGA)

It represents a transient vascular insufficiency of both hippocampi.

This is a rare condition which usually affects people **over the age of 50**.

It lasts **less than 24 hours** and an **awareness of personal identity** is retained, along with normal cognition.

The cause is **unknown** but it may be related to a migrainous phenomenon or transient ischaemia.

It is claimed that the condition may be associated with neuronal loss in the hippocampal area or abnormal metabolism by neurones in this area leading to build up of lactate, but definitive proof does not exist.

#### **TTT is Reassurance.**

**No** specific therapy is required; specifically **no** increased use of anti-platelet agents is needed.

**EX:** A 60-year-old man presents with an episode of memory loss.

Three days earlier he had become **confused**. His wife led him into the house - he apparently sat down at her request, and had a cup of tea. **He then wandered around the house, confused, but remained conscious** and able to have some **conversation with his wife**, though continuing to **ask similar questions repeatedly**.

**After 3 hours**, he abruptly **returned to normal** and had **no recollection** of the events.

### Sciatic nerve palsy

Sciatic nerve palsy is a known complication of a **total hip replacement** (femoral nerve palsy can occur but is much less common).

It causes **global weakness of the ankle** due to the involvement of both of its branches: **tibial nerve (plantarflexion and inversion)** and **common peroneal nerve (dorsiflexion and eversion)**.

The **ankle jerk is absent** due to tibial nerve involvement.

When back pain is caused by a **L5/S1 disc prolapse**, the **S1** nerve root may be affected

The **Achilles reflex tests** the **S1/2** nerve root, and sciatic nerve.

**NB:** Ankle reflex (**tibial nerve** mediated) and

**NB:** Knee reflex (**femoral nerve** mediated).

**NB:** Foot drop >>> affection of **common peroneal nerve**

### Conus medularis syndrome

Conus medularis syndrome presents with **mixed UMNL** and **LMNL** signs.

These include bilateral distal weakness with increased tone and hyper-reflexia, fasciculation. Sensory loss is most marked in the perianal region. It is much rarer than cauda equina syndrome.

Cauda equina syndrome is associated with flaccid paralysis.

Spinal cord infarction related to anterior spinal artery disease presents most frequently with sudden onset pain and loss of power and sensation beginning in the thoracic region. The symptoms seen here have slowly built up over a few weeks and affect a more distal spinal cord distribution.

Sacroiliitis would not be associated with neurological deficit.

	<b>Conus Medullaris Syndrome</b>	<b>Cauda Equina Syndrome</b>
<b>Presentation</b>	Sudden and bilateral	Gradual and may be unilateral leg signs initially
<b>Reflexes</b>	Knee jerks preserved, ankle jerks affected	Both knee and ankle jerks affected
<b>Radicular pain</b>	Less severe	More severe
<b>Sensory</b>	Numbness often localised to perianal area, dissociation can occur, usually bilateral and symmetrical	Numbness often localised to the saddle area, may be asymmetrical and unilateral, sensory loss often dermatomal
<b>Motor</b>	Symmetrical, hyperreflexic distal paresis, less marked than cauda equina, may be fasciculations	Areflexic paraplegic, may be asymmetric, more marked than conus medullaris, fasciculations rare, atrophy more common
<b>Impotence</b>	Frequent	Often less marked
<b>Sphincter dysfunction</b>	Urinary retention and atonic anal sphincter present early in disease (can cause overflow urinary incontinence)	Urinary retention, usually presents later in course of disease
<b>Low back pain</b>	More marked	Less marked

## Glasgow coma scale (GCS)

Eye opening (4)	Verbal response (5)	Motor response (6)
Spontaneously	Orientated	Obeys verbal commands
To speech	Disorientated	Localises painful stimuli
To painful stimulus	Inappropriate words	Withdrawal to pain
No response	Incomprehensible sounds	Flexion to pain
	No response	Extension to pain
		No response

GCS is meaningless unless it is **broken down into its components (E V M)**.

It is important to note that the GCS is unreliable and should not be applied to patients who are inebriated, intubated or who have a therapeutic or traumatic paralysis.

## Miscellaneous:

**Gait disturbance** may occur for a variety of reasons:

- 1) **Sensory** ataxia in B12 deficiency and tabes dorsalis
- 2) **Pyramidal** signs in B12 deficiency and SLE
- 3) **Cerebellar** ataxia in cerebrotendinous xanthomatosis.

**Aphasia:**

- In **Broca's** or **non-fluent** or **expressive** aphasia the patient is unable to name objects with poor comprehension and repetition. It localises to the Broca's area in the left posterior inferior **frontal** gyrus.

- In **Wernicke's** or **fluent** or **receptive** aphasia the patient is able to form correct grammatical sentences but language content is incorrect. It localises to the dominant superior **temporal** gyrus. There is poor comprehension and repetition but verbal output is fluent.

- **Transcortical motor aphasia** which localises to the anterior superior frontal lobe, the patient is able to repeat and have good comprehension and repetition but is unable to express themselves and have halting, effortful speech with intact repetition, Patients also have impaired writing skills.
- **Transcortical sensory aphasia** has impaired auditory comprehension with intact repetition and fluent speech, but the patient is unable to follow verbal commands with fluent grammatical speech. It differs from Wernicke's aphasia in that patients still have intact repetition, and exhibit echolalia (the compulsive repetition of words).
- **Conduction aphasia**. It is characterised by frequent speech errors, impaired repetition, and reduced phonological short-term memory and naming difficulties. In contrast to other forms of dysphasia, speech output is otherwise fluent and grammatically correct. Comprehension is intact.
- **Anomic aphasia** (also known as **nominal aphasia**) results in word finding difficulties. On closer examination there may also be repetition problems and comprehension problems but these are typically mild compared to other aphasia syndromes.
- **Global aphasia** results in **an almost mute patient**: there is poor verbal output, comprehension, repetition and understanding. With deficits in **all** aspects of language: spontaneous speech, naming, repetition, auditory comprehension, reading and writing. It is commonly seen in patients with large infarctions of the left cerebral hemisphere, usually due to occlusion of the internal carotid or middle cerebral artery. The visual centres remain intact and therefore patients are able to follow instructions shown to them.
- **Aphemia** is a type of aphasia in which there is severe dysarthria and impairment of verbal output. There is intact comprehension. It is believed to be the result of pars opercularis, inferior pre-Rolandic gyrus or subcortical lesions.

**Spaces:**

- **Subarachnoid space** is in between the arachnoid mater and the pia mater. Vascular malformations and aneurysms typically bleed in the subarachnoid space e.g. CT shows blood in the Sylvian fissure.
- **Subdural** refers to the area between the dura and the arachnoid.
- **Epidural** is between the skull and the dura.
- **Subgaleal** is a potential space between the skull and the scalp aponeurosis.
- **Subcortical** is in the white matter of the brain below the cortex.



**Lesions:**

- **FTD** (fronto-temporal dementia) appears to begin in the **orbitofrontal cortex** and **anterior cingulate regions** of the frontal lobes, along with the anterior insula.
- Damage to the **hippocampus** and **parahippocampus** results in memory problems and has early involvement in **Alzheimer's** disease.
- The **corpus callosum** can be involved in **multiple sclerosis** where so-called Dawson's fingers can be seen.
- **Prefrontal cortex** damage can result in disinhibition and problems with social interaction and judgement and has been implicated in **schizophrenia**.

The differential diagnoses in a patient presenting with **headaches** and **painful diplopia** are:

- 1) A posterior communicating aneurysm (PCA).
- 2) Ophthalmoplegic migraine.
- 3) Pituitary adenoma/ Apoplexy.
- 4) Cavernous sinus thrombosis, or
- 5) A medical mononeuritis.

**Conventional angiography** is the definitive procedure for the detection and characterisation of cerebral aneurysms.

**Digital subtraction angiography** may be helpful in identifying an acutely ruptured aneurysm.

# Psychiatry



**Unexplained symptoms**

There are a wide variety of psychiatric terms for patients who have symptoms for which no organic cause can be found:

Unexplained symptoms:

- **Somatisation = Symptoms**
- **HypoChondria = Cancer**

**Somatisation disorder:**

- Multiple physical **SYMPTOMS** present for **at least 2 years** and can be associated with **multiple medical admissions**.
- Common symptoms include gastrointestinal (belching, pain, vomiting, nausea), skin (burning, itching, tingling) and sexual and menstrual complaints. They are **not usually bizarre**.
- Somatisation means the expression of psychological distress into bodily complaints for which medical help is sought.
- Patient **refuses** to accept advice or reassurance or negative test results.
- **Her** progress will be slower if she thinks her doctors do not believe her.
- Relatives should be involved, and
- **Empathy**, not persuasion, is the key to management ± antidepressives

**Hypochondrial disorder:**

- Persistent belief in the presence of an underlying serious **DISEASE**, e.g. **Cancer**.
- Patient again refuses to accept reassurance or negative test results.

**Conversion disorder:**

- Typically involves **loss of motor or sensory function**.
- **Some** patients may experience secondary **gain** from loss of function.
- **Psychogenic Aphonia** is a form of conversion disorder: not speaking after a shocking event.
- The patient doesn't consciously feign the symptoms (factitious disorder) or seek material gain (malingering).
- Patients may be indifferent to their apparent disorder - la belle indifference - although this has not been backed up by some studies.

**EX:** An 18-year-old sprinter who is currently preparing for a national athletics meeting. He describes a numb sensation below his knee. On examination the patient there is apparent sensory loss below the right knee in a non-dermatomal distribution. The team doctor suspects a non-organic cause of his symptoms. This is an example of a Conversion disorder.

**EX:** A 16-year-old girl is brought for review by her father. She is talented violinist and is due to start Music College in a few weeks' time. Her parents are concerned she has had a stroke as she is reporting weakness on her right side. Neurological examination is inconsistent and you suspect a non-organic cause for her symptoms. Despite reassurance about the normal examination findings the girl remains unable to move her right arm. What is the most appropriate term for this behaviour? >> This is a typical conversion disorder. There may be underlying tension regarding her musical career which be manifesting itself as apparent limb weakness.

### **Dissociative disorder:**

- Dissociation is a process of 'separating off' certain memories from normal consciousness.
- In contrast to conversion disorder involves **psychiatric symptoms** e.g. Amnesia, fugue, stupor.
- Dissociative identity disorder (DID) is the new term for multiple personality disorder as is the most severe form of dissociative disorder.

### **Munchausen's syndrome:**

- Also known as **factitious disorder**.
- The intentional production of physical or psychological symptoms.

### **Malingering:**

- Fraudulent simulation or exaggeration of symptoms with the intention of financial or other **gain**.

**EX:** A 24-year-old male is admitted to the ED complaining of severe abdominal pain. On examination he is shivering and rolling around the trolley. He has previously been investigated for abdominal pain and no cause has been found. He states that unless he is given morphine for the pain he will kill himself. >> He is malingering as the patient is reporting symptoms with the deliberate intention of getting morphine.

**EX:** A 46-year-old man is seen by an occupation health doctor due to long-term sickness leave. He states chronic lower back pain prevents him from working but examination findings are inconsistent and the doctor suspects a non-organic cause of his symptoms. >>> This is an example of a malingering.

### **Aphonia**

Aphonia describes the inability to speak. Causes include:

- **RLN** Recurrent laryngeal nerve palsy (e.g. Post-thyroidectomy).
- **Psychogenic Aphonia.**

Psychogenic Aphonia is considered to be a form of conversion disorder.

**EX:** A 42-year-old woman presents for review. Her husband reports that she has had an argument with their son which resulted in him leaving home. Since this happened she has not been able to speak. Clinical examination of her throat and chest is unremarkable. This is **Psychogenic Aphonia**.

### **Generalised anxiety disorder (GAD).**

The central feature is excessive worry about a number of different events, associated with heightened tension. Concomitant anxiety and depressive disorders are common and should be looked for.

The goal of intervention should be remission (complete resolution of symptoms), which is associated with better functioning and a lower likelihood of relapse. Such interventions are used in a stepwise fashion:

- 1) **Step one** should be used for all patients with GAD. It involves early identification and assessment of cases, with education about GAD and treatment options and active monitoring.
- 2) **Step two** is used for cases of diagnosed GAD that have not improved after education and active monitoring. Patients should be offered individual non-facilitated self-help or guided self-help and psychoeducational groups.
- 3) **Step three** is used for those patients where there is marked functional impairment or cases which have not improved after step two interventions. Patients should be offered an individual high-intensity psychological intervention (CBT or applied relaxation) or a drug treatment (SSRI).

Verbal and written information should be provided on the likely benefits and disadvantages, and the choice of treatment based on the person's preference (unless there is evidence that one mode of treatment is superior in the individual case).

**Sertraline** has been shown to be the most cost-effective drug but **all SSRIs** (or **SNRIs**) can be considered.

**Pregabalin** can be used when patients are intolerant of SSRIs or SNRIs.

Benzodiazepines should **not** be used except as a short-term measure during crises. Antipsychotics are also not used.

Patients who fail to adequately respond to step three interventions, or those with a risk of self-harm or a significant comorbidity should be referred for specialist treatment.

**EX:** A 35-year-old woman presents with shortness of breath, palpitations and anxiety.

The episodes have been occurring over 3 years, but are worse recently. The episodes occur at stressful periods and are also related to difficult tasks at work. There is no history of drug or alcohol abuse.

The most appropriate pharmacological management for this patient >> **SSRI (Paroxetine) (Seroxat 20 mg tablet).**

### **Body dysmorphic disorder (Dysmorphophobia)**

Body dysmorphic disorder (sometimes referred to as **dysmorphophobia**) is a mental disorder where patients have a significantly distorted body image.

Diagnostic and Statistical Manual (DSM) IV criteria:

- Preoccupation with an imagined defect in appearance. If a slight physical anomaly is present, the person's concern is markedly excessive.
- The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The preoccupation is not better accounted for by another mental disorder (e.g., dissatisfaction with body shape and size in Anorexia Nervosa).

**EX:** A 23-year-old man asks to be referred to a plastic surgeon. He is concerned that his ears are too big in proportion to his face. He reports that he now seldom leaves the house because of this. On examination his ears appear to be within normal limits. The most appropriate description of this behaviour is >> **Dysmorphophobia.**

### **Sleep paralysis**

Sleep paralysis is a common condition characterized by transient paralysis of skeletal muscles which occurs when awakening from sleep or less often while falling asleep.

It is thought to be related to the paralysis that occurs as a natural part of **REM** (rapid eye movement) sleep.

Sleep paralysis is recognised in a wide variety of cultures.

Features:

- 1) **Paralysis** - this occurs **after waking up** or **shortly before falling asleep**.
- 2) **Hallucinations** - images or speaking that appear during the paralysis.

Management:

- If troublesome **clonazepam** may be used.

**EX:** A 23-year-old man presents as he is concerned about a number of recent episodes related to sleep. He finds when he wakes up and less often when he is falling asleep he is 'paralysed' and unable to move. This sometimes associated with what the patient describes as 'hallucinations' such as seeing another person in the room.

**Rapid eye movement (REM) sleep behaviour disorder**, is a parasomnia manifested by **vivid dreams** associated with simple or complex motor behaviour during REM sleep. Polysomnography demonstrates increased electromyographic tone and dream enactment, often associated with the **violent** re-enacting of dreams and occurring when the normal atonicity of REM sleep is lost.

There is an association with the later development of movement disorders and these can be predicted by a number of years.

**Parkinson's disease** is increasingly linked with REM sleep behaviour disorder.

Making the situation safe is paramount but treatment with **clonazepam** is the intervention of choice. Counselling can also play a role.

### Anorexia nervosa (AN): features

The **most common cause** of admissions to child and adolescent psychiatric wards.

Anorexia nervosa is associated with the **abnormal perception of body image**.

Patients generally **feel well despite** the protestations of others who think that they look awful. They exercise avidly and are **often high achievers at school or in the workplace**.

#### Epidemiology:

- **90%** of patients are **female**.
- Predominately affects teenage and young-adult females.
- Prevalence of between 1:100 and 1:200 (i.e. 0.5-1%).

#### Diagnosis (based on the DSM-IV criteria):

- Person chooses not to eat - **BMI < 17.5 kg/m<sup>2</sup>, or < 85% of that expected**.
- **Intense fear of being obese**.
- **Disturbance of weight perception**.
- **Amenorrhoea** = 3 consecutive cycles.

The prognosis of patients with anorexia nervosa remains **poor**.

Up to 10% of patients will eventually die because of the disorder.

Anorexia nervosa is associated with a number of characteristic clinical signs and physiological abnormalities which are summarised below:

#### Anorexia features:

- **Most things low**, Except:
- **3G's and 3C's raised**: growth hormone, glucose, salivary glands, cortisol, cholesterol, carotinaemia.

#### Features:

- Reduced BMI
- Hypotension
- Bradycardia
- Enlarged salivary glands
- Others: excessive physical activity as dancing, academic success, asexual behaviour and OCD.



Physiological abnormalities:

- **Hyponatraemia, Hypokalaemia** (dt laxative and diuretics abuse)
- **Metabolic alkalosis** (dt vomiting),
- **↑ Serum amylase level** (dt frequent vomiting)
- **Normal serum albumin.**
- **Hypocalcaemia** (dt dietary deficiency & associated protein deficiency)
- Low FSH, LH, oestrogens but with **normal testosterone in females.**
- **Low T3**, though **T4 and TSH may be normal**
- **Ferritin** levels are **low** in a state of malnutrition.
- **Normocytic normochromic anaemia** (dt BM depression)
- Raised **growth hormone**
- Impaired **glucose tolerance**
- Raised **cortisol** but are typically within the 'normal range'
- **Hypercholesterolaemia**
- **Hypercarotinaemia**

Other features:



- A phobic avoidance of normal weight
- Over perception of body image
- Relentless dieting.
- Self-induced vomiting.
- Laxative abuse
- Excessive exercise.

- **Amenorrhea:** due to hypogonadotrophic hypogonadism with very mild ↑ serum prolactin.
- **Lanugo hair**
- Loss of axillary and pubic hair.
- Denial الإنكار
- Concealment الأخطاء والتمويه
- Enmeshed families.

Hospitalized patients with anorexia nervosa and **NGT** feeding are at risk of **refeeding syndrome**, which can lead to **profound hypophosphatemia**.

**Refeeding syndrome** is defined as the clinical complications which arise as a consequence of fluid and electrolyte shifts during the nutritional support of malnourished patients.

Refeeding syndrome comprises: **Hypophosphatemia**, **Hypokalaemia**, **Hypomagnesaemia**, Deficiencies in vitamins, for example, thiamine and trace minerals, and Fluid overload with oedema.

**EX:** Female pt. 15 years old has **primary amenorrhoea**, **loss of weight**, low BMI, **occasional diarrhoea**, **anaemia Hb is 10 gm%**, low FSH, low LH, and low Oestradiol but with normal testosterone, normal TSH, **low albumin >>> Coeliac disease not anorexia nervosa.**

### Bulimia nervosa

Bulimia nervosa is a type of eating disorder characterised by episodes of binge eating followed by intentional vomiting.

**EX:** Young female patient has **tooth erosion** associated with **hyponatremia**, **hypokalaemic metabolic alkalosis**, **low urea & hypocalcaemia** with ↑ **ALP**.

If **severe hypokalaemia** with **low urinary K less than 1 mmol/l** (Normal: 25-100 mmol/l) >>> this fits with **laxative abuse** leading to increase GIT K loss and renal conservation of K >>> **Urinary screen for laxatives.**

Management:

- 1) Referral for specialist care is appropriate in all cases.
- 2) Cognitive behaviour therapy (**CBT**) is currently considered **first-line** treatment.

- 3) Interpersonal psychotherapy is also used but takes longer than CBT.
- 4) Pharmacological treatments have a **limited** role - a trial of **high-dose fluoxetine** is currently licensed for bulimia but long-term data is lacking.

### Hypomania vs. mania

The presence of **psychotic symptoms** differentiates mania from hypomania.

Psychotic symptoms:

- 1) **Delusions of grandeur** جنون العظمة
- 2) **Auditory hallucinations**

The following symptoms are common to both hypomania and mania:

Mood:

- Predominately elevated
- Irritable

Speech and thought:

- **Pressured**
- **Flight of ideas**
- Poor attention

Behaviour:

- Insomnia
- Loss of inhibitions: sexual promiscuity, overspending, risk-taking
- Increased appetite

This man's **grandiose delusions**, **flight of ideas** and **pressure of speech** fit best with a diagnosis of **mania**.

Treatment options include mood stabilisers such as:

- Lithium
- Sodium valproate, and
- Carbamazepine.

Other treatment options include atypical anti-psychotics (such as risperidone), and benzodiazepines.

**Schizophrenia: features****Schizophrenia: epidemiology**

Risk of developing schizophrenia:

- **Monozygotic twin** has schizophrenia = **50%**
- Parent has schizophrenia = 10-15%
- Sibling has schizophrenia = 10%
- No relatives with schizophrenia = 1%

Schneider's first rank symptoms may be divided into auditory hallucinations, thought disorders, passivity phenomena and delusional perceptions:

**1) Auditory hallucinations of a specific type:**

- Two or more voices discussing the patient in the third person.
- Thought echo.
- Voices commenting on the patient's behaviour.

**2) Thought disorder (thought alienation):**

- Thought insertion
- Thought withdrawal
- Thought broadcasting

**3) Passivity phenomena:**

- Bodily sensations being controlled by external influence.
- Actions/impulses/feelings - experiences which are imposed on the individual or influenced by others.

**4) Delusional perceptions:**

- A two stage process where first a normal object is perceived then secondly there is a sudden intense delusional insight into the objects meaning for the patient e.g. 'the traffic light is green therefore I am the King'.

**Other features of schizophrenia include:**

- Impaired insight
- **Incongruity**/blunting of affect (**inappropriate emotion for circumstances**)
- Decreased speech
- Neologisms: made-up words
- Catatonia
- Negative symptoms: incongruity/blunting of affect, anhedonia (inability to derive pleasure), alogia (poverty of speech), avolition (poor motivation).

Schizophrenia occurs **twice** as often in **unmarried** and **divorced** people as in married or widowed individuals.

Schizophrenia is commoner in individuals in **unstable relationships**

Furthermore, people with schizophrenia are 8 times more likely to be in the **lowest socioeconomic** groups.

These statistics are likely to reflect the alienating effects of this disease rather than any causal relationship or risk factor associated with poverty or a single life.

Nevertheless, **low income** and **poverty** may increase the risk for exposure to **biological factors** (for example, infections or toxins) or **social stressors** that could trigger the illness in susceptible people.

Monozygotic twins may have a 50% concordance and 10% of offspring may be affected suggesting **strong inheritance**.

**Amphetamines** are known to lead to **drug induced schizophrenia** >> A 28-year old man complained of voices which told him to self-harm.

**Schizophrenia: prognostic indicators:**

Factors associated with **poor** prognosis: ☹

- 1) **Strong family history**
- 2) **Gradual** onset
- 3) **Low IQ**
- 4) Premorbid history of **social withdrawal**
- 5) **Lack of obvious precipitant**

**Schizophrenia: management**

NICE published guidelines on the management of schizophrenia.

Key points:

- **Oral atypical antipsychotics** are **first-line**.
- **Cognitive behavioural therapy (CBT)** should be offered to **all** patients.
- Close attention should be paid to cardiovascular risk-factor modification due to the high rates of cardiovascular disease in schizophrenic patients (linked to antipsychotic medication and high smoking rates).

**Concrete thinking:** when a patient can't use abstraction to understand the meaning of a sentence. It is more common in schizophrenia.

**Literal thinking** is of course a feature of autism.

**Antipsychotics**

Antipsychotics act as **dopamine D2 receptor antagonists**, blocking dopaminergic transmission in the mesolimbic pathways.

Conventional antipsychotics are associated with problematic extrapyramidal side-effects which has led to the development of atypical antipsychotics such as clozapine.

**Extrapyramidal side-effects:**

- 1) **Parkinsonism**.
- 2) **Acute dystonia** (e.g. torticollis, oculogyric crisis).
- 3) **Akathisia** (severe **restlessness**).
- 4) **Tardive dyskinesia** (late onset of choreoathetoid movements, abnormal, involuntary, may occur in 40% of patients, may be irreversible, most common is chewing and pouting of jaw).

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in **elderly patients**:

- Increased risk of **stroke**
- Increased risk of **venous thromboembolism**

Antipsychotics in the **elderly** - increased risk of **stroke** and **VTE**.

Anticholinergics used to treat dystonia might make akathisia worse.

Benzodiazepines (traditionally clonazepam) have the best research evidence in combating this unpleasant side effect of Akathisia.

**Other side-effects:**

- 1) Antimuscarinic: dry mouth, blurred vision, urinary retention, constipation.
- 2) Sedation
- 3) Weight gain
- 4) Raised prolactin: galactorrhoea.
- 5) **Impaired glucose tolerance**
- 6) **Neuroleptic malignant syndrome**: pyrexia, muscle stiffness
- 7) Reduced seizure threshold (greater with atypicals)
- 8) **Prolonged QT interval** (particularly haloperidol)
- 9) **Others: Depression, Anxiety.**

### **Atypical antipsychotics**

Atypical antipsychotics should now be used **first-line** in patients with **schizophrenia**, according to 2005 NICE guidelines.

They **block serotonin receptors** (especially the **5-HT<sub>2</sub>** subtype) as well as **D<sub>2</sub> dopamine receptors**.

The receptor affinity (K<sub>i</sub>) values are 0.4 and 3.13 nM for 5-HT<sub>2A</sub> and D<sub>2</sub> receptors respectively (i.e. highest affinity for **Serotonin 5-HT<sub>2A</sub> receptor**).

The main advantage of the atypical agents is a significant reduction in extrapyramidal side-effects.

Conventional antipsychotics are associated with problematic extrapyramidal side-effects which has led to the development of atypical antipsychotics.

Adverse effects of atypical antipsychotics:

- 1) **Weight gain** (It is an extremely common adverse effect of atypical antipsychotics such as **Olanzapine**). وزن
- 2) **Clozapine** is associated with **agranulocytosis** (see below). (Fup **CBC**).
- 3) **Olanzapine** have been implicated in **precipitating diabetes** and **DKA**.

- 4) The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in **elderly** patients:
- Increased risk of **stroke** (especially olanzapine and risperidone).
  - Increased risk of **venous thromboembolism**.

Examples of atypical antipsychotics:

- Clozapine
- Olanzapine (Zyprexa ®)
- Risperidone (Risperdal ®)
- Quetiapine (Seroquel ®)
- Amisulpride

Clozapine, one of the first atypical agents to be developed, carries a significant risk of agranulocytosis and **CBC** monitoring is therefore essential during ttt.

For this reason clozapine should only be used in patients resistant to other antipsychotic medication.

Adverse effects of clozapine:

- 1) Agranulocytosis (1%), Neutropenia (3%).
- 2) Reduced seizure threshold - can induce seizures in up to 3% of patients.

**Clozapine is no longer used first-line due to the risk of agranulocytosis.**

### **Neuroleptic malignant syndrome (NMS)**

It is a **rare** but **dangerous** condition seen in patients taking **antipsychotic** medication (e.g. Olanzapine haloperidol, chlorpromazine and Citalopram).

It carries a mortality of up to 10% and can also occur with **atypical antipsychotics**.

It may also occur with **dopaminergic drugs (such as levodopa)** for **Parkinson's** disease, usually when the **drug is suddenly stopped** or **the dose reduced**.

It is thought to arise from blockage of dopamine receptors or decrease in availability of dopamine (↓ **Dopamine**).

Primary diagnostic features are altered conscious level, autonomic instability and muscular rigidity with raised CPK

It can occur **within hours** of initiating drug therapy, but typically takes about **1 week**.

The mortality is between 10-20%.



Features:

- More common in **young male** patients
- **Onset** usually in **first 10 days of treatment** or **after increasing dose of antipsychotic.**
- **Pyrexia**
- **Altered mental status**
- **Muscle rigidity** (sometimes with dysphagia and dysarthria).
- **Extrapyramidal signs, tremors, catatonia, muteness.**
- **Tachycardia**
- **Autonomic dysfunction.**
- A raised **CPK & AST** is present in most cases.
- A **leucocytosis** may also be seen.
- **Renal failure** may occur secondary to rhabdomyolysis
- **Metabolic acidosis.**
- **DIC.**

Management:

- **Stop** antipsychotic.
- **IV fluids** to prevent renal failure.
- **Bromocriptine, Dopamine agonist.**
- **Dantrolene IV** was formerly recommended as monotherapy, case series suggests that when it is used in the absence of Bromocriptine, mortality may actually be increased.

**Dantrolene** is thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum.

**EX:** A 35-year-old man with a history of schizophrenia is brought to the ED by worried friends due to drowsiness. On examination he is generally rigid. >>> A diagnosis of neuroleptic malignant syndrome should be suspected.

**Post-traumatic stress disorder (PTSD)**

PTSD can develop in people of any age following a traumatic event, for example a major disaster or childhood sexual abuse or sudden death of his small children.

It encompasses what became known as '**shell shock**' following the First World War.

One of the DSM-IV diagnostic criteria is that symptoms have been present for more than one month.

In PTSD the **onset** of symptoms is usually **delayed** and it tends to run a **prolonged course**.

Features:

- 1) **Re-experiencing:** **flashbacks**, **nightmares**, repetitive and distressing intrusive images.
- 2) **Avoidance:** avoiding people, situations or circumstances resembling or associated with the event.
- 3) **Hyperarousal:** hypervigilance for threat, exaggerated startle response, sleep problems, **insomnia**, **irritability** and **difficulty concentrating**.
- 4) **Emotional numbing** - lack of ability to experience feelings, feeling detached.
- 5) **Depression**.
- 6) Drug or alcohol misuse.
- 7) Anger.
- 8) Unexplained physical symptoms

Management:

- Following a traumatic event single-session interventions (often referred to as debriefing) are not recommended.
- Watchful waiting may be used for mild symptoms lasting less than 4 weeks.
- Military personnel have access to ttt provided by the armed forces.
- **Trauma-focused cognitive behavioural therapy (CBT) or Eye Movement Desensitisation and Reprocessing (EMDR) therapy** may be used in more severe cases.
- Drug treatments for PTSD should **not** be used as a routine **first-line** treatment for adults. If drug treatment is used then **Paroxetine (Seroxat®)** or **Mirtazapine (Remeron®)** are recommended.

### **Post-concussion syndrome**

Post-concussion syndrome is seen after **even minor** head trauma.

Typical features include:

- **Headache**
- Fatigue
- Anxiety/depression
- Dizziness

### **Depression: screening and assessment**

#### **Screening:**

The following two questions can be used to screen for depression:

- 'During the last month, have you often been bothered by feeling down, depressed or hopeless?'
- 'During the last month, have you often been bothered by having little interest or pleasure in doing things?'

A 'yes' answer to either of the above should prompt a more in depth assessment.

#### **Assessment:**

There are many tools to assess the degree of depression including the Hospital Anxiety and Depression (HAD) scale and the Patient Health Questionnaire (PHQ-9).

#### **Hospital Anxiety and Depression (HAD) scale:**

- Consists of 14 questions, 7 for anxiety and 7 for depression
- Each item is scored from 0-3
- Produces a score out of 21 for both anxiety and depression
- Severity: 0-7 normal, 8-10 borderline, 11+ case
- Patients should be encouraged to answer the questions quickly

#### **Patient Health Questionnaire (PHQ-9):**

- Asks patients 'over the last 2 weeks, how often have you been bothered by any of the following problems?'
- 9 items which can then be scored 0-3

- Includes items asking about thoughts of self-harm
- Depression severity: 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe

**NICE** use the **DSM-IV** criteria to grade depression:

- 1. Depressed mood most of the day, nearly every day.
- 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
- 3. Significant weight loss or weight gain when not dieting or decrease or increase in appetite nearly every day.
- 4. Insomnia or hypersomnia nearly every day.
- 5. Psychomotor agitation or retardation nearly every day.
- 6. Fatigue or loss of energy nearly every day.
- 7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
- 8. Diminished ability to think or concentrate, or indecisiveness nearly every day.
- 9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

<b>Sub threshold depressive symptoms</b>	Fewer than 5 symptoms.
<b>Mild depression</b>	Few, if any, symptoms in excess of the 5 required to make the diagnosis, and symptoms result in only minor functional impairment.
<b>Moderate depression</b>	Symptoms or functional impairment are between 'mild' and 'severe'.
<b>Severe depression</b>	Most symptoms, and the symptoms markedly interfere with functioning. Can occur with or without psychotic symptoms.

**Early morning waking** is a classic somatic symptom of depression and often develops earlier than general insomnia.

### **Suicide**

Factors associated with risk of suicide following a deliberate self-harm:

- **Efforts to avoid discovery**
- **Planning**
- Leaving a written note
- Final acts such as sorting out finances
- Violent method

These are in addition to standard **risk factors for suicide**:

- 1) **Male** sex
- 2) **Advancing** age  $\geq 45$  years old.
- 3) Unemployment or social isolation
- 4) Living **alone** (especially if separated, **divorced**, or **widowed**)
- 5) History of **mental illness** (depression, schizophrenia)
- 6) Suffering from a personality disorder
- 7) Previous history of psychiatric treatment
- 8) History of deliberate **self-harm**
- 9) Alcohol or drug misuse
- 10) A previous attempt which resulted in hospital admission
- 11) Criminal record
- 12) Lower social class.

About **one-third** of people who attempt suicide will **repeat** the attempt **within one year**, and about 10% of those who threaten or attempt suicide eventually do kill themselves.

### **Seasonal affective disorder (SAD)**

It describes depression which occurs predominately around the **winter** months. Bright light therapy has been shown to be more effective than placebo for patients with SAD.

### Post-partum mental health problems

It ranges from the 'baby-blues' to puerperal psychosis.

The **baby-blues** which is seen in around **two-thirds of women**. Whilst **poor sleeping** can be a sign of depression it is to be expected with a **new** baby.

The **Edinburgh Postnatal Depression Scale (EPNDS)** may be used to screen for depression:

- 10-item questionnaire, with a maximum score of 30.
- Indicates how the mother has felt over the previous week.
- Score > 13 indicates a 'depressive illness of varying severity'.
- Sensitivity and specificity > 90%.
- Includes a question about self-harm.

'Baby-blues'	Post-natal depression	Puerperal psychosis
Seen in around (2/3) <b>60-70% of women</b> .	Affects around <b>10%</b> of women.	Affects approximately 0.2% of women.
Typically seen <b>3-7 days following birth</b> and is more common in <b>primiparous</b> .	(affect 100 - 150 women per 1000 births)	Onset usually within the <b>first 2-3 weeks</b> following birth.
Mothers are characteristically <b>anxious, poor sleeping, tearful</b> and <b>irritable</b> .	Most cases start within a <b>month</b> and typically peaks at 3 months.	Features include severe swings in mood (similar to <b>bipolar</b> disorder) and disordered perception (e.g. auditory <b>hallucinations</b> ).
	Features are similar to depression seen in other circumstances.	

'Baby-blues'	Post-natal depression	Puerperal psychosis
Explanation, <b>Reassurance</b> and support, the health visitor has a key role.	As with the baby blues <b>reassurance</b> and support are important.  <b>Cognitive behavioural therapy (CBT)</b> may be beneficial.  Certain <b>SSRIs</b> such as <b>Paroxetine</b> and <b>Sertraline</b> may be used if symptoms are severe; whilst they are secreted in breast milk it is not thought to be harmful to the infant.	<b>Admission to hospital</b> is usually required.  <b>Good prognosis.</b>  There is around a <b>20%</b> risk of <b>recurrence</b> following future pregnancies.

**Paroxetine** is recommended by SIGN because of the low milk/plasma ratio. Fluoxetine is best avoided due to a long half-life.

### Selective serotonin reuptake inhibitors (SSRIs)

SSRIs are considered first-line treatment for the majority of patients with depression.

- **Citalopram** (see below: QT interval) and **Fluoxetine (Prozac®)** are currently the preferred SSRIs.
- **Sertraline (Zoloft ®)** is useful in **Post MI** myocardial infarction as there is more evidence for its safe use in this situation than other antidepressants.
- **Citalopram** and **Sertraline** appear to be the **safest** antidepressants to prescribe **with warfarin**.
- SSRIs should be used with caution in children and adolescents. Fluoxetine is the drug of choice when an antidepressant is indicated.

**Adverse effects:**

- 1) **Gastrointestinal symptoms** are the most common side-effect.
- 2) There is an increased risk of **gastrointestinal bleeding** in patients taking SSRIs. A PPI should be prescribed if a patient is also taking a NSAID.
- 3) Patients should be counselled to be vigilant for **increased anxiety and agitation** after starting a SSRI.
- 4) Fluoxetine and Paroxetine have a higher propensity for **drug interactions**.
- 5) **SSRI >>>> SIADH >>> Hyponatraemia**.

SSRI + NSAID >>> GI bleeding risk >>> so, give a PPI.
---

**Citalopram and the QT interval:**

- The Medicines and Healthcare products Regulatory Agency (MHRA) released a warning on the use of citalopram in 2011.
- It is advised that citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval
- The maximum daily dose is now 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment.

**Interactions:**

- 1) **NSAIDs / Aspirin**: NICE guidelines advise 'do not normally offer SSRIs', but if given co-prescribe a proton pump inhibitor.
- 2) **Warfarin / heparin**: NICE guidelines recommend avoiding SSRIs and considering mirtazapine (Remeron®).
- 3) **Triptans**: avoid SSRIs.

Following the initiation of antidepressant therapy patients should normally be **reviewed by a doctor after 2 weeks**.

For **patients under the age of 30 years** or **at increased risk of suicide** they should be **reviewed after 1 week**.

If a patient makes a good response to antidepressant therapy they should continue on treatment for **at least 6 months after remission** as this **reduces the risk of relapse**. Patients should be reassured that antidepressants are not addictive.



When stopping a SSRI the dose should be **gradually reduced over a 4 week (شهر) period** (this is not necessary with fluoxetine).

**Paroxetine (Seroxat ®)** has a higher incidence of discontinuation symptoms than other SSRIs.

Discontinuation symptoms (SSRI Discontinuation Syndrome):

**(Serotonin syndrome):**

Symptoms can occur within days and can last months following withdrawal and then disappear.

1) **Psychiatric:**

- Increased mood change
- Confusion, agitation, hypomania, anxiety, and
- Difficulty sleeping
- **Sweating**
- **Coma**

2) **Neurological:**

- **Hyperthermia, hyperreflexia, myoclonus ataxia, unsteadiness**
- **Restlessness, hallucination, up to seizures.**
- **Paraesthesia**
- **Mydriasis**
- Headache, dizziness

3) **GIT symptoms:** pain, cramping, **nausea, vomiting, diarrhoea.**

4) **Hypertension, tachycardia, pyrexia**

5) **DIC** (↓ PLT, ↑PT, ↑ PTT, ↓Fibrinogen).

It is thought that shorter acting SSRIs, when discontinued or when the dosage is lowered, produce **an "anticholinergic rebound,"** interrupting the production of the acetylcholine.

TTT of serotonin syndrome (SSRI overdose):

- **No specific treatment is given.**
- **Supportive.**

- BDZ to reduce agitations.
- Serotonin antagonists (cyproheptadine or methysergide)
- BP control.
- Hyperthermia control.

### Tricyclic antidepressants (TCAs)

TCAs are used less commonly now for depression due to their side-effects and toxicity in overdose.

They are however used widely in the treatment of neuropathic pain, where smaller doses are typically required.

Some author are considering prescribing a TCA for a patient who has not responded to two different types of SSRIs.

Common side-effects (Antimuscarinic side-effects are more common with **Imipramine** than other types of TCA):

- 1) **Drowsiness**
- 2) **Dry mouth**
- 3) **Blurred vision**
- 4) **Constipation**
- 5) **Urinary retention** (so take care especially in old man with BPH)

Choice of tricyclic:

- Low-dose amitriptyline is commonly used in the management of neuropathic pain and the prophylaxis of headache (both tension and migraine).
- **Amitriptyline** (tryptizole®) and **Dosulepin** (Dothiepin) (Prothiadine 75mg) are considered **the most dangerous in overdose**.
- **Lofepramine** has a **lower incidence of toxicity in overdose**.

More sedative	Less sedative
Amitriptyline Dosulepin Clomipramine Trazodone*	<b>Imipramine</b> Lofepramine Nortriptyline

\*Trazodone is technically a 'tricyclic-related antidepressant'

### Tricyclic overdose

Overdose of tricyclic antidepressants (TCA) is a common presentation to emergency departments.

**Amitriptyline (Tryptizole ®)** and **Dosulepin (Dothiepin) (Prothiadine 75mg)** are particularly dangerous in overdose.

Early features relate to **anticholinergic properties**: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include:

- 1) Anticholinergic effects: mydriasis, dry skin, dry mouth, urinary retention, constipation, confusion.
- 2) Confusion, seizures and coma
- 3) Metabolic acidosis
- 4) Arrhythmias & ECG changes include:
  - 1) Sinus tachycardia
  - 2) **Widening of QRS**
  - 3) **Prolongation of QT interval >> VT**

Widening of **QRS > 100ms** is associated with an increased risk of **seizures** whilst **QRS > 160ms** is associated with **ventricular arrhythmias**.

Management:

- 1) **IV (NaHCO<sub>3</sub>) 50 mmol**: may reduce the risk of seizures and arrhythmias in severe toxicity.
- 2) TTT of Arrhythmias:
  - **Lignocaine**: it increases the electrical stimulation threshold of the ventricle, suppressing the automaticity of conduction and terminating VT, it should be emphasized that **correction of acidosis is the first line in management** of tricyclic induced **arrhythmias**.
  - Class 1A antiarrhythmic (e.g. Quinidine) and class IC (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III (as amiodarone) should also be avoided as they prolong the QT interval.
- 3) Dialysis is ineffective in removing TCA.

**EX.** Pt with **TCA overdose** (e.g. amitriptyline) with marked **tachycardia >>>** the **first** step would be to >>> obtain an **ECG**. If changes such as **QRS widening** are seen then **IV bicarbonate** should be given.

An ECG would immediately indicate if there is a risk of significant TCA toxicity by showing a wide QRS complex or abnormal axis deviation.

TCA overdose >>> give **IV Na bicarbonate (NaHCO<sub>3</sub>)**

**Amiodarone** is best **avoided** in TCA overdose as it may increase the risk of torsade due to QT prolongation.

**NB:** Arrhythmias following tricyclic overdose are difficult to treat as many commonly used anti-arrhythmic are contraindicated. **The use of sodium bicarbonate has been shown to be effective, even in patients who are not acidotic.** This is a rare occasion where NaHCO<sub>3</sub> IV is recommended as first line therapy, here for VT/QRS widening in TCA poisoning. It provides exogenous Na to overcome the competitive fast Na channel blockade produced by TCA, and produces an alkalaemia (or reverses acidaemia) that mitigates the fast Na channel blockade by the TCA ingested.

### **Chronic fatigue syndrome (CFS)**

It is diagnosed after at least 4 months of disabling fatigue affecting mental and physical function more than 50% of the time in the absence of other disease which may explain symptoms.

#### **Epidemiology:**

- More common in **females**.
- Past psychiatric history has not been shown to be a risk factor.

In general, in order to receive a **diagnosis** of chronic fatigue syndrome, a patient must satisfy **two criteria**.

**First**, they must have **severe chronic fatigue of 6 months or longer duration** with other known **medical** conditions **excluded** by clinical diagnosis.

**Secondly**, they must concurrently have 4 or more of the following symptoms:

Fatigue is the central feature, other recognised **features** include:

- Sleep disorders.
- Muscle and/or Multi-joint pain without swelling or redness.
- Headache of a new type

- Painful LN without enlargement.
- Sore throat.
- Cognitive dysfunction: difficulty thinking, inability to concentrate, impairments of short-term memory.
- General malaise or flu like symptoms.
- Dizziness
- Nausea
- Palpitations

**Investigations:**

NICE guidelines suggests carrying out a large number of screening blood tests to exclude other pathology e.g.: CBC, ESR, CRP, U&E, LFT, RBS, TFT, Calcium, Ferritin, coeliac disease screening and urine analysis.

**Management:**

- **CBT**: very effective, number needed to treat = 2
- Graded exercise therapy: a formal supervised program, don't advice to go to the gym.
- Low dose amitriptyline may be useful for poor sleep.
- Referral to pain management clinic if pain is a predominant feature.

Good prognosis in children

**Restless leg syndrome (RLS)**

It is a **spontaneous continuous** lower limb movements that may be associated with **paraesthesia**.

It is extremely common, affecting between **2 – 10%** of the general population.

Males and females are **equally** affected and a family history may be present.

**Clinical features:**

- Uncontrollable urge to move legs (akathisia). Symptoms initially occur at night but as condition progresses may occur during the day.
- Symptoms worse at rest.
- Paraesthesias e.g. crawling or throbbing sensations.
- Movement during sleep may be noted by the partner: periodic limb movements of sleeps (PLMS).

**Causes and associations:**

- 1) There is **+ve family history** in **50%** of patients with **idiopathic** RLS.
- 2) **Iron deficiency anaemia (IDA)**.

- 3) **Uraemia.**
- 4) **DM**
- 5) **Pregnancy**

The diagnosis is clinical although CBC to exclude IDA may be appropriate.

**Management:**

- Simple measures: walking, stretching, massaging of affected limb.
- TTT IDA
- Dopamine agonists are first line of ttt: **Pramipexole (Sifrol®)**, **Ropinirole (Requip®)**.
- BDZ
- Gabapentin

**Obsessive Compulsive Disorder OCD (obsessional neurosis)**

It is associated with rituals, fears (for example, hurting others but rarely carried out), thoughts abhorrent to the patient and ruminations. **Patients maintain good insight** and often find the illness distressing (which can lead to depression).

It typically starts in **early adult life** and has equal sex incidence. The **intelligence** of patients is often **above average**.

Sigmund Freud postulated that obsessive compulsive symptoms were caused by **rigid toilet-training practices**, however this theory is **no** longer widely accepted.

Pathophysiology:

- Some research suggest **childhood group A beta-haemolytic streptococcal infection** may have a role.

Associations:

- 1) **Depression** (30%)
- 2) **Schizophrenia** (3%)
- 3) Sydenham's **chorea**
- 4) **Tourette's syndrome**
- 5) **Anorexia nervosa**

### Cognitive behavioural therapy (CBT)

Main points:

- Useful in the management of **depression** and **anxiety** disorders.
- Can be used for patients already taking antidepressants.
- Usually consists of **one to two hour sessions once per week**.
- **Should be completed within 6 months**.
- Patients usually get around **16-20 hours in total**.

### Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) is a useful treatment option for patients with severe depression refractory to medication or those with psychotic symptoms.

Short-term side-effects:

- **Headache**
- **Nausea**
- Short term **memory** impairment: Memory loss of events prior to ECT
- **Cardiac arrhythmia**
- **Musculoskeletal injury (Crush fracture of the vertebral bodies)** has been reported after ECT, but with adequate anaesthetisation, this is rare.

Long-term side-effects:

- Some patients report impaired memory

Although ECT, by definition, causes a controlled seizure there is **NO increased risk of epilepsy in the long-term**.

The **only absolute contraindications** is **raised intracranial pressure**.

Although ECT has been safely used one month following a stroke, it is advisable to avoid treatment in the first three months.

Most guidelines state that a **recent CVA (within 1 to 3 months)** is a **contraindication**.

**ECT** would usually be **avoided** in a **recent cerebrovascular accident**.

### Functional disorder

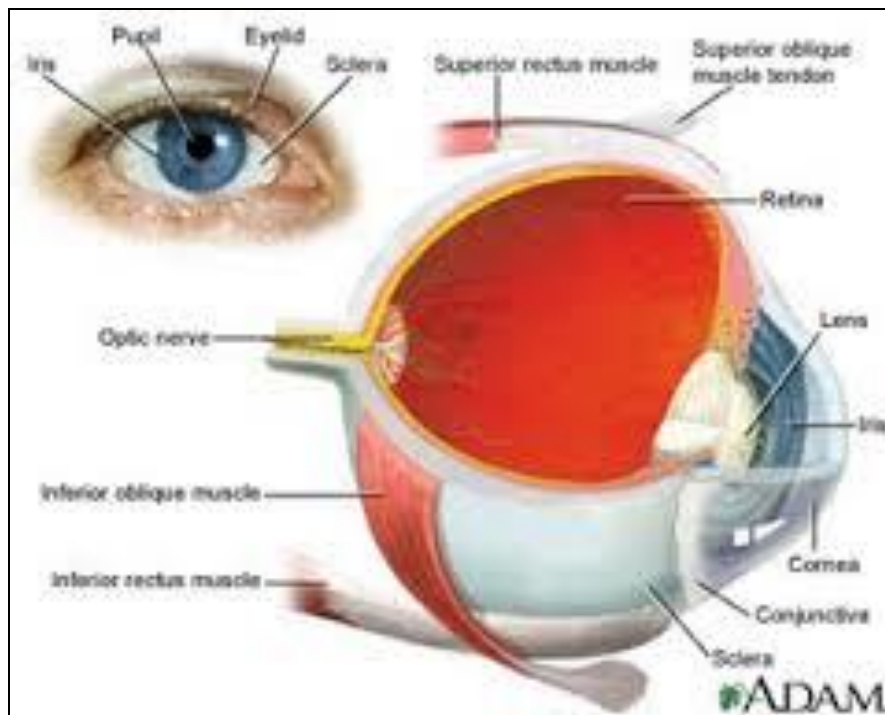
Functional refers to an illness that is **without a structural defect**.

Organic brain syndromes are physical conditions including structural brain disease and metabolic disturbances causing mental dysfunction.

**Mutism** is the most likely of the symptoms described to be associated with a functional disorder but is associated with schizophrenia or autism.



# Ophthalmology



**Age related macular degeneration**

It is **the most common cause of blindness** in the **UK**.

Degeneration of the central retina (macula) is the key feature with changes usually bilateral.

Traditionally two forms of macular degeneration are seen:

- 1) **Dry** (geographic atrophy) macular degeneration: characterised by **Drusen** - yellow round spots in Bruch's membrane.
- 2) **Wet** (exudative, neovascular) macular degeneration: characterised by choroidal neovascularisation. Leakage of serous fluid and blood can subsequently result in a rapid loss of vision. Carries **Worst** prognosis.

<b>Drusen = Dry macular degeneration</b>
--

Recently there has been a move to a more updated classification (based on fluorescein angiography):

- 1) **Early** age related macular degeneration (non-exudative, age related Maculopathy): drusen and alterations to the retinal pigment epithelium (RPE)
- 2) **Late** age related macular degeneration (neovascularisation, exudative).

Risk factors:

- Age: most patients are **over 60 years of age**
- **Female** sex
- **Smoking**
- Family history
- More common in **Caucasians**
- High cumulative sunlight exposure

Macular degeneration >> <b>smoking</b> is risk factor
---

Features:

- ↓ Visual acuity: '**blurred**', '**distorted**' vision, central vision is affected first.
- **Central** scotomas
- **Fundoscopy**: **drusen**, pigmentary changes.

Investigation and diagnosis:

- 1) Optical coherence **tomography**: cross sectional views of the macula.
- 2) **If neovascularisation** is present >>> **fluorescein angiography** is performed.

Management:

1) General:

- **Stop smoking.**
- Having a balanced diet, with plenty of fresh fruits and vegetables may also slow the progression of macular degeneration.
- High dose of **antioxidants** (beta-carotene, vitamins C and E, and zinc) **may** help to slow down visual loss for patients with established macular degeneration. Supplements should be **avoided** in **smokers** due to an increased risk of **lung cancer**.

Beta-carotene has been found to increase the risk of lung cancer and hence antioxidant dietary supplements are not recommended for smokers.

2) Dry macular degeneration: Do not have current medical treatments.

3) Wet macular degeneration:

- Photocoagulation
- Photodynamic therapy
- Anti-vascular endothelial growth factor (anti-VEGF) treatments: intravitreal Ranibizumab.

### Diabetic retinopathy

It is **the most common cause of blindness** in **adults aged 35-65 years-old**.

Diabetic retinopathy occurs in **both** type 1 and 2 DM and may be a presenting feature in type 2 as the **condition may have existed for many years prior** to diagnosis.

Progression may be slowed with **improved** both **glycaemic** and **hypertensive control** but the latter has been shown to be **more** effective at reducing progression (UKPDS).

There are no data at present to suggest that statin therapy reduces disease progression.

**Hyperglycaemia** is thought to cause increased retinal blood flow and abnormal metabolism in the retinal vessel walls. This precipitates damage to endothelial cells and pericytes.

Endothelial dysfunction leads to increased vascular permeability which causes the characteristic exudates seen on fundoscopy.

**Pericytes dysfunction** predisposes to the formation of **microaneurysms**.

**Neovascularization** is thought to be caused by the production of growth factors in response to retinal ischaemia.

**Despite** quite **marked** new vessel disease the **visual acuity may be normal**.

In exams you are most likely to be asked about the characteristic features of the various stages/types of diabetic retinopathy.

Recently a new classification system has been proposed, dividing patients into those with non-proliferative diabetic retinopathy (**NPDR**) and those with proliferative retinopathy (**PDR**):

Traditional classification	New classification
<p><b><u>Background retinopathy:</u></b></p> <ol style="list-style-type: none"> <li>1) Microaneurysms (MA) (dots)</li> <li>2) Blot haemorrhages (<math>\leq 3</math>)</li> <li>3) Hard exudates (HE): collections of exudated lipid and protein</li> <li>4) Seen in <b>both</b> type 1 &amp; 2 DM</li> </ol> <p><b><u>Pre-proliferative retinopathy:</u></b></p> <ol style="list-style-type: none"> <li>1) Cotton wool spots (CWS): (soft exudates; ischaemic infarcts of the nerve fibre layer of the retina)</li> <li>2) <math>&gt; 3</math> blot haemorrhages</li> <li>3) Venous beading/looping</li> <li>4) Deep/dark cluster haemorrhages</li> <li>5) More common in <b>Type I DM</b>, treat with laser photocoagulation.</li> </ol>	<p><b><u>Mild NPDR:</u></b></p> <ul style="list-style-type: none"> <li>• 1 or more microaneurysm</li> </ul> <p><b><u>Moderate NPDR:</u></b></p> <ul style="list-style-type: none"> <li>• Microaneurysms</li> <li>• Blot haemorrhages</li> <li>• Hard exudates</li> <li>• Cotton wool spots,</li> <li>• Venous beading/looping and</li> <li>• Intraretinal microvascular abnormalities (IRMA) less severe than in severe NPDR</li> </ul> <p><b><u>Severe NPDR:</u></b></p> <ul style="list-style-type: none"> <li>• Blot haemorrhages and microaneurysms in 4 quadrants</li> <li>• Venous beading in at least 2 quadrants</li> <li>• IRMA in at least 1 quadrant</li> </ul>

Prevalence	Risk factors
<ul style="list-style-type: none"> <li>➤ 2-6% of background retinopathy.</li> <li>➤ 20-60% pre-proliferative retinopathy.</li> <li>➤ 70-75% of proliferative cases</li> </ul>	<ul style="list-style-type: none"> <li>➤ ↑HbA1C</li> <li>➤ Proteinuria.</li> <li>➤ Duration of DM</li> </ul>

### Proliferative retinopathy:

- Retinal **neovascularisation** - may lead to vitreous haemorrhage
- Fibrous tissue forming anterior to retinal disc
- More common in **Type I DM**, 50% blind in 5 years
- **Normal visual acuity** is seen in **proliferative retinopathy**.
- **Urgent** referral to **ophthalmologist** for **panretinal photocoagulation**.

### Maculopathy:

- Based on **location** rather than severity, **anything is potentially serious**
- **Hard exudates** and other 'background' changes on macula.
- Check visual acuity.
- More common in **Type II DM**.

**Microaneurysm** on **fluorescein angiography** is the **earliest** sign of **Diabetic Nephropathy**.

**Asymmetric DM Retinopathy >>> suspect ocular ischaemia (carotid artery disease)**

**In T1DM >> Urgent** referral to an ophthalmologist (seen within one week) is required if there is **proliferative** retinopathy or there is evidence of clinically significant **macular oedema** (**hard exudates** at the fovea).

### Screening:

- **T1 DM:**
  - Newly diagnosed DM → after 5 years
  - From 5-10 years → annual
  - More than 10 years → 6 monthly
- **T2 DM:**
  - Annually

## Optic atrophy

Optic atrophy is seen as pale, well demarcated disc on fundoscopy.

It is usually bilateral and causes a gradual loss of vision.

Strictly speaking optic atrophy is a descriptive term, it is the **optic neuropathy that results in visual loss**.

Causes may be acquired or congenital.

### Acquired causes:

- 1) **Multiple sclerosis**
- 2) **Papilloedema (longstanding)**
- 3) **Raised IOP** intraocular pressure (e.g. **glaucoma**, tumour)
- 4) **Retinal damage** (e.g. choroiditis, **retinitis pigmentosa**)
- 5) **Ischaemia**
- 6) **Toxins: Tobacco amblyopia, Methanol, Arsenic, Lead, Quinine**
- 7) **Nutritional:** Vitamin B1, B2, B6 and B12 deficiency

### Congenital causes:

- 1) **Friedreich's ataxia**
- 2) **Mitochondrial disorders e.g. Leber's optic atrophy**
- 3) **DIDMOAD** - the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome).

## Optic neuritis

Causes:

1) <b>M.S. (Multiple sclerosis)</b>	2) <b>DM</b>	3) <b>Syphilis</b>
-------------------------------------	--------------	--------------------

Features:

- 1) **Unilateral** decrease in visual acuity over hours or days
- 2) **Poor discrimination of colours, 'red desaturation'**
- 3) **Pain worse on eye movement**
- 4) Relative **afferent** pupillary defect
- 5) **Central scotoma**

Optic neuropathy does **not** cause any abnormalities of the shape or size of the pupil. However the **light reaction is diminished**. **Accommodation is normal**.

Optic neuritis is described as being rarely associated with **diclofenac** therapy.

Optic neuritis is **very rare** in people **over the age of 50**.

Sudden visual loss due to optic neuritis is very unusual.

Management:

- High-dose steroids
- Recovery usually takes 4-6 weeks

Prognosis:

- **MRI:** if > 3 white-matter lesions, 5-year risk of developing multiple sclerosis is c. 50%

**EX:** A 26-year-old man presented with a **24 hour history of blurred vision** in the left eye and mild left frontal **headache**. He had a 10 year history of **DM**.

Examination of the left eye revealed a **central scotoma**.

The most likely diagnosis is >>> **Optic neuritis**.

**NB:** In a **young diabetic** the aetiology is usually an **embolus** of the central retinal artery or one of its branches. However there is **pain** associated with this visual loss, namely **headache**.

**NB:** **Occlusion of the central retinal artery (CRAO)** or one of its branches which supplies the macular region will result in almost **immediate** diminution or **loss** of visual acuity in the involved eye and is usually **Painless**.

### Retrobulbar Neuritis

It is inflammation **behind optic nerve head**, **the optic disc is normal**.

**Patient see nothing, Doctor see nothing**

Features:

- Loss of visual acuity
- Afferent pupillary defect during swinging flashing light
- ↓ Colour vision (red looks pallor).

### Angioid retinal streaks

Angioid retinal streaks are seen on fundoscopy as **irregular dark red streaks radiating from the optic nerve head**.

They are caused by degeneration, calcification and breaks in Bruch's membrane. .

Causes:

- 1) **Paget's disease**
- 2) **Sickle-cell anaemia**
- 3) **Acromegaly**
- 4) **Ehler-Danlos syndrome**
- 5) **Pseudo-xanthoma elasticum**

### Retinitis pigmentosa

It primarily affects **the peripheral retina** resulting in **funnel vision** (Tunnel vision).

Features:

- **Night blindness** is often the initial sign
- **Funnel vision** (the preferred term for tunnel vision)
- Fundoscopy: black bone spicule-shaped pigmentation in the peripheral retina, mottling of the retinal pigment epithelium.(see picture)

**Retinitis pigmentosa >> Night blindness + Funnel vision**

Associated diseases:

- 1) **Refsum disease**: cerebellar ataxia, peripheral neuropathy, deafness, ichthyosis
- 2) **Alport's syndrome**
- 3) **Abetalipoproteinemia**
- 4) **Usher syndrome**
- 5) **Lawrence-Moon-Biedl syndrome**
- 6) **Kearns-Sayre syndrome**

N.B: Ocular manifestations of tuberose sclerosis includes retinal hamartomas



### Relative afferent pupillary defect (Marcus-Gunn pupil)

Also known as the **Marcus-Gunn pupil**, a relative afferent pupillary defect is found by the '**swinging light test**'.

It is caused by a **lesion anterior to the optic chiasm** i.e. optic nerve or retina.

Causes:

- **Retina:** detachment
- **Optic nerve:** optic neuritis e.g. multiple sclerosis

Pathway of pupillary light reflex:

- **Afferent:** retina → optic nerve → lateral geniculate body → midbrain
- **Efferent:** Edinger-Westphal nucleus (midbrain) → oculomotor nerve.

Examination of the pupils using a light shone alternately in each eye reveals that when the light is shone in the right eye both pupils constrict but when the light source immediately moves to the left eye both eyes appear to dilate.>> Left optic neuritis.

This is the 'swinging light test' and reveals a relative afferent pupillary defect. As there is a defect in the afferent nerve on the left side the pupils constrict less than normal, giving the impression of dilation.

In young female age, multiple sclerosis causing optic neuritis is the likely underlying diagnosis. Optic neuritis typically causes a dull ache in the region of the eye which is aggravated by movement.

### Sudden painless loss of vision

The most common causes of a **sudden painless loss** of vision are as follows:

- 1) **Ischaemic optic neuropathy** e.g. **temporal arteritis** or atherosclerosis
- 2) Occlusion of central retinal **vein**
- 3) Occlusion of central retinal **artery**
- 4) **Vitreous haemorrhage**
- 5) **Retinal detachment**

**Amaurosis fugax:** classically described as a **transient monocular** vision loss, it develops over seconds, remains for up to 5 minutes and resolves over 10-20 minutes, that appears as a "curtain coming down vertically into the field of vision in one eye". Sometimes it occurs as episodes, caused by ipsilateral carotid artery disease.

The only feature that differentiates the middle cerebral artery syndrome from the carotid artery syndrome is amaurosis fugax.

In **elderly** people **giant cell arteritis** is a **common presentation** of **acute monocular visual loss**.

**1) Ischaemic optic neuropathy (ION):**

- May be due to **Arteritic** i.e. **arteritis** (e.g. temporal arteritis) or **non-arteritic** i.e. **atherosclerosis** (e.g. HTN, DM older patient).
- Due to occlusion of the **short posterior ciliary arteries**, causing damage to the optic nerve.
- Altitudinal field defects are seen → loss of vision above or below the horizontal level.
- Commonly the symptoms **are first noticed upon awakening in the morning**. The other eye may suffer a similar event within five years.

**Sudden** onset of **painless monocular visual loss** in patients **aged 50 or more** is commonly due to **ischaemic optic neuropathy (ION)**.

**2) Central retinal vein occlusion (CRVO):**

- Incidence increases with age, **more common than arterial** occlusion.
- Causes: **glaucoma, polycythaemia, hypertension**.
- **Severe** retinal haemorrhages are usually seen on fundoscopy.

Central retinal vein occlusion (**CRVO**) >> **sudden painless loss of vision + severe retinal haemorrhages** on fundoscopy

EX: A 65-year-old man with a history of primary open-angle glaucoma (**POAG**) presents with **sudden painless loss of vision** in his right eye. On examination of the right eye the optic disc is swollen with **multiple flame-shaped and blot haemorrhages**. What is the most likely diagnosis>> **CRVO**

### 3) Central retinal artery occlusion (CRAO):

- Due to thromboembolism (from atherosclerosis) or arteritis (e.g. temporal arteritis).
- Features include afferent pupillary defect, '**cherry red**' spot over a pale and opaque retina.

### 4) Vitreous haemorrhage:

- Causes: **DM**, bleeding disorders.
- Features may include sudden visual loss, dark spots.
- **Flashes of light or floaters** are symptoms of vitreous detachment. If present in **long standing DM** >> patient is at risk of retinal detachment.

### 5) Retinal detachment:

- Features of vitreous detachment, which may precede retinal detachment, include **flashes of light or floaters** (see below).

Flashes and floaters of light >>> Vitreous/Retinal detachment

**Differentiating posterior vitreous detachment, retinal detachment and vitreous haemorrhage:**

Posterior vitreous detachment	Retinal detachment	Vitreous haemorrhage
<b>Flashes</b> of light (photopsia) - in the <b>peripheral</b> field of vision. <b>Floaters</b> , often on the temporal side of the central vision.	Dense shadow that starts <b>peripherally</b> progresses towards the central vision. A veil or curtain over the field of vision. Straight lines appear curved (+ve Amsler grid test). Central visual loss.	Large bleeds cause sudden visual loss. Moderate bleeds may be described as numerous dark spots. Small bleeds may cause floaters.

The history of diabetes, complete loss of vision in the affected eye and inability to visualise the retina point towards a diagnosis of vitreous haemorrhage.

## **Glaucoma**

Glaucoma is a group disorders characterised by optic neuropathy due, in the majority of patients, to raised intraocular pressure (IOP).

It is now recognised that a minority of patients with raised IOP do not have glaucoma and vice versa.

### **Acute angle closure glaucoma (AACG)**

In acute angle closure glaucoma (AACG) there is a rise in IOP secondary to an impairment of aqueous outflow.

#### **Factors predisposing to AACG include:**

- **Hypermetropia** (long-sightedness)
- Pupillary dilatation
- Lens growth associated with age
- **Mydriatic eye drops**
- Drugs which may precipitate acute glaucoma include **anticholinergics** and **TCA**.

Acute angle <b>closure</b> glaucoma ( <b>AACG</b> ) is associated with <b>Hypermetropia</b> , Whereas primary <b>open</b> -angle glaucoma ( <b>POAG</b> ) is associated with <b>myopia</b> .
---

#### **Features:**

- 1) **Severe pain:** may be ocular or headache
- 2) Decreased visual acuity
- 3) Symptoms worse with **Mydriasis** (e.g. watching TV in a dark room)
- 4) Hard, **red eye**
- 5) Haloes around lights
- 6) **Semi-dilated non-reacting pupil**
- 7) Corneal oedema results in dull or hazy cornea
- 8) **Systemic** upset may be seen, such as nausea and vomiting and even abdominal pain

**Management:**

- Urgent referral to an ophthalmologist
- Management options include reducing aqueous secretions with **acetazolamide** and inducing pupillary constriction with **topical pilocarpine**.

Treatment of acute glaucoma (AACG) >> **Acetazolamide IV + Pilocarpine ED**

**EX:** A 68-year-old man with a history of **type 2 DM** presents with worsening eye sight. **Mydriatic drops** are applied and fundoscopy reveals pre-proliferative diabetic retinopathy (**PPDR**). A referral to ophthalmology is made. Later in the evening whilst driving home he develops **pain** in his left eye associated with **decreased visual acuity**. What is the most likely diagnosis? >> **AACG**, as **Mydriatic drops** are a **known precipitant of acute angle closure glaucoma**. This scenario is more common in exams than clinical practice.

**Primary open-angle glaucoma (POAG): management**

Primary open-angle glaucoma (POAG), also referred to as **(chronic simple glaucoma)** is present in around 2% of people older than 40 years.

Other than age, **risk factors** include:

- 1) **Family history**
- 2) **Black patients**
- 3) **Myopia**
- 4) **HTN**
- 5) **DM**

POAG may present insidiously and for this reason is often detected during routine optometry appointments. Features may include:

- **Peripheral** visual field loss - **nasal scotomas (Loss of nasal visual field)** progressing to '**tunnel vision**'
- Decreased visual acuity
- Optic disc cupping

The majority of patients with POAG are managed with eye drops.

These aim to lower IOP which in turn has been shown to prevent progressive loss of visual field.

Surgery in the form of a trabeculectomy may be considered in refractory cases.

Medication	Mode of action	Notes
Prostaglandin analogues (e.g. <b>Latanoprost</b> )	Increases uveoscleral outflow	Once daily administration. It Should be used <b>first</b> -line in patients with a history of <b>asthma</b> . Adverse effects include brown pigmentation of the iris.
Miotics (e.g. <b>Pilocarpine</b> , a muscarinic receptor agonist)	Increases uveoscleral outflow	Adverse effects included a constricted pupil, headache and blurred vision.
Beta-blockers (e.g. <b>Timolol</b> )	Reduces aqueous production	Should be avoided in asthmatics and patients with heart block
Carbonic anhydrase inhibitors (e.g. <b>Dorzolamide, Diamox</b> )	Reduces aqueous production	Systemic absorption may cause sulphonamide-like reactions
Sympathomimetic (e.g. <b>brimonidine</b> , an alpha2-adrenoceptor agonist)	Reduces aqueous production and increases outflow	Avoid if taking MAOI or TCA. Adverse effects include hyperaemia

## Cataracts

Majority	Systemic:	Ocular
1) <b>Aging</b> 2) <b>UV light</b>	1) <b>DM</b> 2) <b>Steroids</b> 3) Infection (congenital rubella) 4) <b>Metabolic</b> <ul style="list-style-type: none"> <li>○ <b>Hypocalcaemia</b></li> <li>○ <b>Galactosaemia</b></li> </ul> 5) <b>Myotonic dystrophy</b> 6) <b>Down's syndrome</b>	<ul style="list-style-type: none"> <li>• <b>Trauma</b></li> <li>• <b>Uveitis</b></li> <li>• High <b>myopia</b></li> <li>• Topical steroids</li> </ul>

Classification:

- 1) **Nuclear**: change lens refractive index, common in old age
- 2) **Polar**: localized, commonly inherited, lie in the visual axis
- 3) **Subscapular**: due to steroid use, just deep to the lens capsule, in the visual axis
- 4) **Dot opacities**: common in normal lenses, also seen in diabetes and myotonic dystrophy

## Red eye

There are many possible causes of a red eye.

It is important to be able to recognise the causes which require urgent referral to an ophthalmologist.

Below is a brief summary of the key distinguishing features.

Red eye >> glaucoma or uveitis?

- Glaucoma: severe pain, haloes, 'semi-dilated' pupil, Hazy cornea
- Uveitis: small, fixed oval pupil, ciliary flush

**1) Acute angle closure glaucoma (AACG):**

- **Severe pain** (may be **ocular** or **headache**)
- Decreased visual acuity, patient sees **haloes**
- **Semi-dilated pupil**
- **Hazy cornea**

**2) Anterior uveitis:**

- Acute onset
- pain
- Blurred vision and photophobia
- **Small, fixed oval pupil, ciliary flush**

**3) Scleritis:**

- **Severe pain** (may be worse on movement) and tenderness
- May be underlying **autoimmune** disease e.g. rheumatoid arthritis

**4) Conjunctivitis:**

- Purulent discharge if bacterial, clear discharge if viral

**5) Subconjunctival haemorrhage:**

- history of trauma or coughing bouts

**Tunnel vision**

Tunnel vision is the concentric diminution of the visual fields.

Causes:

- 1) **Papilloedema**
- 2) **Glaucoma**
- 3) **Retinitis pigmentosa**
- 4) **Choroidoretinitis**
- 5) **Retinal panphotocoagulation.**
- 6) **Optic atrophy** secondary to **Tabes dorsalis**
- 7) **Hysteria**



### Miosis

Causes of miosis (small pupil):

- 7) **Horner's syndrome**
- 8) **Argyll-Robertson pupil**
- 9) Pontine haemorrhage
- 10) Congenital
- 11) Senile miosis

Drugs causes:

- **Opiates**
- **Organophosphate toxicity**
- Parasympathomimetics: pilocarpine

**Argyll-Robertson pupil**: small irregular pupils that do not react to light but react to near accommodation.

Referred to as the “**Whore’s Eye**” because of the association with tertiary syphilis and because of the convenient **mnemonic** that, like a **prostitute**, they “**can accommodate but do not react**”.

**Another mnemonic** used for the Argyll-Robertson Pupil (**ARP**) is Accommodation Reflex Present (**ARP**) but Pupillary Reflex Absent (**PRA**).

Causes: Multiple sclerosis, sarcoidosis, DM.

### Mydriasis

Causes of Mydriasis (large pupil):

- **Third nerve palsy**
- **Holmes-Adie pupil**
- **Traumatic iridoplegia**
- **Phaeochromocytoma**
- **Congenital**

Drug causes of Mydriasis:

- Topical Mydriatic: tropicamide, **atropine**
- Sympathomimetic drugs: amphetamines, **cocaine**, **ethylene glycol**.
- Anticholinergic drugs: TCA

**Hippus** is papillary athetosis. It is typically a **benign** finding. It is a **spasmodic rhythmical dilation and contraction of the pupil**. It is particularly noticeable when pupils are tested with a **light**, but is independent of eye movements or light. Pathological hippus is rare but is recognised with aconite poisoning, trauma, cirrhosis and renal disease (possibly due to frontal lobe dysfunction).

### **Holmes-Adie pupil**

Holmes-Adie pupil is a **benign** condition most commonly seen in **women**. It is one of the differentials of a dilated pupil.

Over years it gradually diminishes in size actually to be smaller than the non-affected pupil.

Holmes ADie = **D**ilated pupil, females, absent leg reflexes.

Overview:

- **Unilateral** in **80%** of cases
- **Dilated pupil**
- Once the pupil has constricted it remains small for an abnormally long time
- **Slowly reactive to near / accommodation reflex**
- But **very poorly (if at all) to light**

Holmes-Adie syndrome:

- Association of Holmes-Adie pupil with **absent ankle/knee reflexes**.

At the beginning of the condition the pupil is large, but over time becomes small and poorly reactive.

**Slit lamp examination** may reveal small worm like contractions of the iris,

But the **usual diagnostic test is to use weak pilocarpine eye drops**, which induce **vigorous pupil contraction** on the **affected** side, but only weak contraction of the pupil on the unaffected side.

### Horner's syndrome

Features:

- 5) **Ptosis.**
- 6) **Miosis** (small pupil).
- 7) **Anhydrosis** (loss of sweating one side).
- 8) **Enophthalmos:** (sunken eye): (in reality the appearance is due to a narrow palpebral aperture rather than true Enophthalmos).

Causes: **(STC)**

Central lesions	Pre-ganglionic lesions	Post-ganglionic lesions
Anhydrosis of the face, arm and trunk	Anhydrosis of the <b>face</b>	<b>No anhydrosis</b>
<b>Stroke</b> <b>Syringomyelia</b> Multiple sclerosis Tumour Encephalitis	Pancoast's tumour Thyroidectomy Trauma Cervical rib	<b>Carotid artery dissection</b> <b>Carotid aneurysm</b> <b>Cavernous sinus thrombosis</b> <b>Cluster headache</b>

Horner's syndrome - **Anhydrosis** determines site of lesion:

- Head, arm, trunk = central lesion: stroke, Syringomyelia.
- Just face = pre-ganglionic lesion: Pancoast's, cervical rib.
- Absent = post-ganglionic lesion: carotid artery.

Distinguishing between causes:

- **Heterochromia** (difference in **iris colour**): seen in **congenital Horner's**
- Anhydrosis: see before.

## Ptosis

Ptosis may be unilateral or bilateral.

Causes of <b><u>bilateral</u></b> ptosis:	Causes of <b><u>unilateral</u></b> ptosis, as bilateral causes plus:
1) <b>Myotonic dystrophy.</b> 2) <b>Myasthenia gravis</b> 3) <b>Syphilis.</b> 4) <b>Congenital.</b>	1) <b>Horner's</b> 2) <b>Third nerve palsy</b>

\*Ptosis is much more common in myasthenia gravis than Lambert-Eaton syndrome

## Third nerve palsy

Features:

- 5) **Eye is deviated 'down and out'** (divergent squint).
- 6) **Ptosis.**
- 7) **Mydriasis** (Pupil may be dilated) (sometimes called a 'surgical' third nerve palsy).
- 8) **Unreactive** pupil to **light**.
- 9) **Pain if** due to a posterior communicating artery aneurysm.

Ptosis + **Miosis** (Constricted pupil) >>> **Horner's Syndrome**

Ptosis + **Mydriasis** (Dilated pupil) >>> **3 rd. Nerve palsy**

Causes:

- DM
- Vasculitis e.g. temporal arteritis, SLE
- False localizing sign due to uncus herniation through tentorium if raised ICP
- **Posterior communicating artery aneurysm** (pupil dilated)
- Cavernous sinus thrombosis
- **Weber's syndrome:** Ipsilateral third nerve palsy with contralateral hemiplegia -caused by midbrain strokes (cerebral peduncle).
- Other possible causes: amyloid, multiple sclerosis

\*This term is usually associated with sixth nerve palsies but it may be used for a variety of neurological presentations.

**Painful third nerve palsy = posterior communicating artery aneurysm** (i.e. EX. Third nerve palsy with headache and meningism >>> should exclude posterior communicating artery aneurysm).

### Herpes zoster ophthalmicus (HZO)

HZO describes the reactivation of the varicella zoster virus (VZV) in the area supplied by the ophthalmic division of the trigeminal nerve. It accounts for around 10% of cases of shingles.

Features:

- Vesicular rash around the eye, which may or may not involve the actual eye itself.
- **Hutchinson's sign**: rash on the tip or side of the nose. Indicates nasociliary involvement and is a **strong risk factor for ocular involvement**.

VZV >> Hutchinson's sign which is strongly predictive for ocular involvement.

Management (Ocular involvement requires **urgent ophthalmology review**):

- **Oral antiviral treatment for 7-10 days**, ideally started within 72 hours.
- **Topical** antiviral treatment is **NOT** given in HZO.
- **Oral corticosteroids** may reduce the duration of pain but do not reduce the incidence of post-herpetic neuralgia.

Complications:

- Ocular: conjunctivitis, keratitis, Episcleritis, anterior uveitis.
- Ptosis
- Post-herpetic neuralgia

### Herpes simplex keratitis

It most commonly presents with a **dendritic corneal ulcer**.

Features:

- **Red, painful eye**
- **Photophobia**

- **Epiphora** (continually streaming tears)
- Visual acuity may be decreased
- **Fluorescein staining** may show **an epithelial ulcer with dendritic pattern of staining (dendritic corneal ulcer)**.

Management:

- Immediate referral to an ophthalmologist
- **Topical acyclovir**
- Giving a topical steroid in this situation could be disastrous as it may worsen the infection.

### Band keratopathy

It is a corneal disease derived from the appearance of calcium on the central cornea caused by **calcium deposition in bowman's layer**.

This is an example of **metastatic calcification**, which by definition, occurs in the presence of **hypercalcaemia**.

Symptoms: Pain and ↓ visual acuity.

TTT: the calcium can be scraped off the cornea or removed with a laser. This can restore sight, but it can take a number of months for normal vision to return as the cornea will be damaged during operation. This can't be repeated too many times as it would make the cornea thinner and thinner.

### Blepharitis

Blepharitis is inflammation of the eyelid margins.

It may due to either **meibomian** gland dysfunction (common, posterior Blepharitis) or **seborrhoeic dermatitis/staphylococcal** infection (less common, anterior Blepharitis).

Blepharitis is also more common in patients with **acne rosacea**.

The meibomian glands secrete oil on to the eye surface to prevent rapid evaporation of the tear film.

Any problem affecting the meibomian glands (as in blepharitis) can hence cause drying of the eyes which in turns leads to irritation.

Features:

- Symptoms are usually **bilateral**
- Grittiness and discomfort, particularly around the eyelid margins
- Eyes may be sticky in the morning
- Eyelid margins may be red. **Swollen eyelids may be seen in staphylococcal blepharitis**
- Styes and chalazions are more common in patients with blepharitis.
- Secondary conjunctivitis may occur

Management:

- 1) Softening of the lid margin using **hot compresses** twice a day.
- 2) **Mechanical removal of the debris from lid margins** - cotton wool buds dipped in a mixture of cooled boiled water and baby shampoo is often used, an alternative is sodium bicarbonate, a teaspoonful in a cup of cooled water that has recently been boiled
- 3) **Artificial tears** may be given for symptom relief in people with dry eyes or an abnormal tear film.
- 4) **Topical Antibiotic Eye drops** if swollen eyelids.

### Lacrimal duct problems

**Dacryocystitis** is infection of the lacrimal sac.

Features:

- **Watering eye (epiphora)**
- **Swelling and erythema at the inner canthus of the eye**

Management is with systemic antibiotics. Intravenous antibiotics are indicated if there is associated periorbital cellulitis.

**Congenital lacrimal duct obstruction** affects around 5-10% of newborns. It is bilateral in around 20% of cases.

Features:

- Watering eye (even if not crying)
- Secondary infection may occur
- Symptoms resolve in 99% of cases by 12 months of age.

**Thyroid eye disease**

Thyroid eye disease affects between **25-50%** of patients with **Graves'** disease.

Pathophysiology:

- It is thought to be caused by an autoimmune response against an autoantigen, possibly the **TSH receptor** → retro-orbital inflammation.
- The inflammation results in glycosaminoglycan and collagen deposition in the muscles.

Prevention (**Avoid**):

- 1) **Smoking** is the **most important modifiable risk factor** for the development of thyroid eye disease.
- 2) **Radioiodine treatment** may **increase** the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help reduce the risk.

Features:

- The patient may be eu-, hypo- or hyperthyroid at the time of presentation
- Exophthalmos
- Conjunctival oedema
- Optic disc swelling
- Ophthalmoplegia
- Inability to close the eye lids may lead to sore, dry eyes.
- If **severe** and **untreated** patients can be at risk of >> **exposure keratopathy** (**Eye is red, painful and ↓ V/A**).

Management:

- Topical lubricants: to prevent corneal inflammation caused by exposure.
- Steroids.
- Radiotherapy.
- Surgery.



**Monitoring patients with established thyroid eye disease:**

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for **urgent review by an ophthalmologist**:

- 1) **Unexplained deterioration in vision**
- 2) **Awareness of change in intensity or quality of colour vision** in one or both eyes
- 3) History of eye suddenly 'popping out' (**globe subluxation**)
- 4) Obvious **corneal opacity**
- 5) **Cornea still visible** when the eyelids are closed
- 6) **Disc swelling**

---

**Temporal arteritis**

---

It is large vessel vasculitis which overlaps with polymyalgia rheumatica (PMR).

Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.

Features:

- Typically patient > 60 years old
- Usually rapid onset (e.g. < 1 month)
- Headache (found in 85%)
- Jaw claudication (65%)
- Visual disturbances secondary to **anterior ischemic optic neuropathy**
- Tender, palpable temporal artery
- Features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- Also lethargy, depression, low-grade fever, anorexia, night sweats

Investigations:

- Raised inflammatory markers: ESR > 50 mm/hr (note ESR < 30 in 10% of patients). CRP may also be elevated
- Temporal artery biopsy: skip lesions may be present
- Note creatine kinase and EMG normal

Treatment:

- **High-dose prednisolone** - there should be a **dramatic response**, if not the diagnosis should be reconsidered.
- **Urgent** ophthalmology review. Patients with visual symptoms should be seen the same-day by an ophthalmologist. Visual damage is often irreversible.

EX: A 74-year-old man presents with a severe throbbing headache on the right side of his head. He has now had this pain for around 6-7 days but reports no obvious trigger. There have been no visual disturbances or episodes of limb weakness. Neurological examination is unremarkable. The right side of his head is tender to touch but he cannot remember falling. >>> It is **temporal arteritis** >>> the most important initial step is to **give high-dose oral prednisolone** to prevent ocular complications.

### Rheumatoid arthritis: ocular manifestations

Ocular manifestations of rheumatoid arthritis are common, with 25% of patients having eye problems.

Ocular manifestations:

- 1) **Keratoconjunctivitis sicca (most common)**, It is **usually bilateral** and associated more with dryness, burning and itch.
- 2) Keratitis
- 3) Corneal ulceration
- 4) **Episcleritis** (erythema)
- 5) **Scleritis** (erythema and **pain**)

The difference between Scleritis and Episcleritis is the presence of **pain**.

**Scleritis is painful,**

Episcleritis is not painful.

Iatrogenic:

- Steroid-induced cataracts
- Chloroquine retinopathy

### **Marfan's syndrome**

Marfan's syndrome is an **autosomal dominant** connective tissue disorder.

It is caused by a defect in the **fibrillin-1 gene** on **chromosome 15** and affects **around 1 in 3,000 people**.

Features:

- Tall stature with arm span to height ratio > 1.05
- High-arched palate
- Arachnodactyly
- Pectus excavatum
- Pes planus
- Scoliosis of > 20 degrees
- Heart: **dilation of the aortic sinuses (seen in 90%)** which may lead to aortic aneurysm, aortic dissection, aortic regurgitation, **mitral valve prolapse (75%)**.
- Lungs: repeated pneumothoraxes
- Eyes: **Upwards lens dislocation (Superotemporal ectopia lentis)** which seen in around **50%** of patients, **blue sclera, and myopia**.
- Dural ectasia (ballooning of the dural sac at the lumbosacral level)

The life expectancy of patients used to be around 40-50 years.

With the advent of regular echocardiography monitoring and beta-blocker/ACE-inhibitor therapy this has improved significantly over recent years.

Aortic dissection and other cardiovascular problems remain the leading cause of death however.

### **Homocystinuria**

Homocystinuria is a **rare autosomal recessive** disease caused by **deficiency of cystathionine beta synthase**.

This results in an accumulation of homocysteine which is then oxidized to homocystine.

Features:

- Often patients have fine, fair hair
- Musculoskeletal: may be similar to Marfan's - Arachnodactyly etc.
- **Neurological** patients may have learning difficulties, seizures.
- Ocular: Downwards (Inferonasal) dislocation of lens
- ↑ **risk of arterial and venous thromboembolism**
- Also malar flush, livedo reticularis

Diagnosis is made by the **cyanide-nitroprusside test**, which is also positive in cystinuria.

Treatment is supplementation of **vitamin B6 (pyridoxine)**.

**Marfan's syndrome >>> Upwards lens dislocation (Superotemporal ectopia lentis)**

While, **Homocystinuria >>> Downwards (Inferonasal) dislocation of lens.**

### Wernicke's encephalopathy

Wernicke's encephalopathy is a neuropsychiatric disorder caused by **thiamine deficiency** which is most commonly seen in **alcoholics**.

Rarer causes include: persistent vomiting, stomach cancer, dietary deficiency.

A **classic triad** of **nystagmus**, **ophthalmoplegia** and **ataxia** may occur.

In Wernicke's encephalopathy **petechial haemorrhages** occur in a variety of structures in the **brain** including the mamillary bodies and ventricle walls.

Features:

- 1) **Nystagmus** (the most common **ocular** sign)
- 2) **Ophthalmoplegia**
- 3) **Ataxia**
- 4) **Confusion**, altered GCS
- 5) Peripheral sensory **neuropathy**

The most commonly found ocular abnormality in patients with Wernicke's encephalopathy is >>> **Nystagmus**.

Investigations:

- Decreased red cell transketolase
- MRI

Treatment is with **urgent replacement of thiamine**

### Foster Kennedy's syndrome

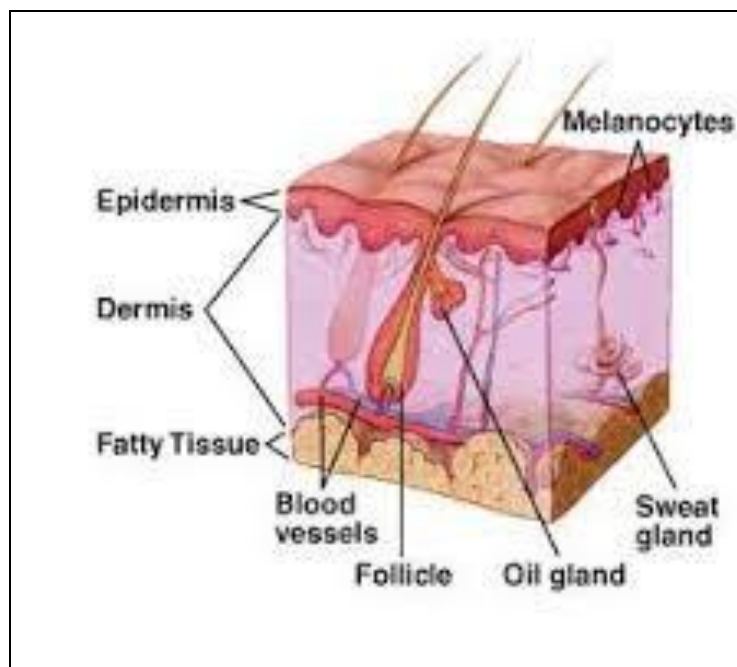
It is a combination of **optic atrophy** and **central scotoma**, **contralateral papilloedema** and **anosmia**.

It is caused by **optic and olfactory nerve compression** and **raised intracranial pressure**.

This is often secondary to a mass such as an olfactory groove meningioma.

Patients may also have other symptoms of raised intracranial pressure such as nausea and vomiting, and frontal symptoms such as emotional lability and memory loss.

# Dermatology



## Epidermis

The epidermis is the outermost layer of the skin and is composed of a stratified squamous epithelium with an underlying basal lamina.

It may be divided into **five** layers:

Layer	Description
Stratum corneum	Flat, dead, scale-like cells filled with keratin Continually shed
Stratum lucidum	Clear layer - present in thick skin only
Stratum granulosum	Cells form links with neighbours
Stratum spinosum	Squamous cells begin keratin synthesis Thickest layer of epidermis
<b>Stratum germinativum</b>	The <b>basement membrane</b> - single layer of columnar epithelial cells <b>Gives rise to keratinocytes</b> Contains <b>melanocytes</b>

## Skin terminology

**Macule:** a **flat** area of altered skin colour is irrespective of the size.

**Papule** is a **raised** lesion **less** than 1 cm in diameter.

**Plaque:** a skin lesion that is **raised** and **greater** than 1 cm in diameter.

**Ulcer** is a discontinuity of the skin with complete loss of the epidermis and often portions of the dermis and subcutaneous fat.

**Vesicle** is a fluid-filled, well-circumscribed raised lesion.

**Pustules** are **small elevations** of the skin containing cloudy or purulent material, usually consisting of necrotic inflammatory cells.

**Bullae** are **large vesicles** containing **serous** fluid.

**Fissures** are cracks in the skin that are narrow but deep.

**Telangiectasias** are collections of enlarged capillaries visible on the skin or mucous membranes.

**Lichenification** of the skin is due to **epidermal thickening** characterised by visible and palpable thickening of the skin with **accentuation of skin markings**.

**Atrophy** of the skin may be due to loss of epidermis, dermis or subcutaneous tissue. Thinning of the epidermis presents as skin that appears thin and translucent. Thinning of the dermis and subcutaneous tissue leads to a depression in the skin.

### **Lichen planus**

It is a skin disorder of **unknown** aetiology, most probably being immune mediated.

Features:

- **Itchy, papular** rash most common on the **palms, soles, genitalia** and **flexor surfaces of arms (e.g. flexor aspect of the wrist)**.
- Rash often **polygonal** in shape (**violaceous papules**), 'white-lace' pattern on the surface (Wickham's striae).
- **Koebner phenomenon**: (new skin lesions appearing at the site of trauma).
- **Oral** involvement in around **50%** of patients.
- **Nails**: thinning of nail plate, longitudinal ridging.
- It typical affects patients aged **30-60 years**.

Lichen:

- **Planus**: purple, pruritic, papular, polygonal rash on flexor surfaces. Wickham's striae over surface. Oral involvement common.
- **Sclerosus**: itchy white spots typically seen on the vulva of elderly women.

Lichenoid drug eruptions - causes:

- Gold
- Quinine
- Thiazides

Management:

- **Topical steroids** are the mainstay of treatment (e.g. **Clobetasone butyrate "Eumovate cream®"**).
- Extensive lichen planus may require oral steroids or immunosuppression.



### **Lichen sclerosis**

Lichen sclerosis was previously termed lichen sclerosis et atrophicus.

It is an inflammatory condition which usually affects the **genitalia** and is more common in **elderly females**.

Lichen sclerosis leads to **atrophy of the epidermis** with **white plaques** forming.

Features:

- **Itch** is prominent.
- A biopsy is often performed to exclude other diagnoses

Management:

- Topical steroids and emollients.
- **Increased risk of vulval cancer.**

**EX:** A 85-year-old lady presents to dermatology clinic complaining of itchy white plaques affecting her vulva. There is no history of vaginal discharge or bleeding. A similar plaque is also seen on her inner thigh. What is the likely diagnosis? >>>  
Lichen sclerosis.

### **Skin disorders associated with pregnancy**

**Polymorphic eruption of pregnancy** (see picture)

- Pruritic condition associated with last trimester
- Lesions often first appear in abdominal striae
- Management depends on severity: emollients, mild potency topical steroids and oral steroids may be used

**Pemphigoid gestationis:** (see picture)

- Pruritic **blistering** lesions.
- Often develop in **peri-umbilical region**, later **spreading** to the trunk, back, buttocks and arms.
- Usually presents 2nd or 3rd trimester and is **rarely seen in the first pregnancy**.
- **Oral corticosteroids** are usually required.

**Shin lesions (see pic)**

The differential diagnosis of shin lesions includes the following conditions:

1. **Erythema nodosum**
2. **Pyoderma gangrenosum**
3. **Pretibial myxoedema**
4. **Necrobiosis lipoidica diabetorum**

Below are the characteristic features: (see pictures):

**1) Erythema nodosum (EN):**

- **Overview:**
  - **Inflammation of subcutaneous fat.**
  - Typically causes **symmetrical, tender, erythematous, nodular** lesions.
  - Usually occurs over shins, may also occur elsewhere (e.g. forearms, thighs).
  - It is **self-limiting** and usually **resolves within 6 weeks**.
  - Lesions **heal without scarring**.
  - Sometimes in severe cases Colchicine (SE: diarrhoea), Thalidomide (teratogenic), Dapsone, Corticosteroids, or K iodide can be used.

**Erythema nodosum (EN)>> Heal without scarring within 1-2 months (6 wk)**

Thalidomide is secreted in **semen**, so the **male** should use **barrier** contraception until at least 1 week after cessation of ttt.

**Woman** must provide a pregnancy test 24 hrs prior to beginning thalidomide therapy because of the very great risk of **teratogenicity**.

If male take thalidomide >>> so he should use barrier contraception and his wife should use effective contraception also.

- **Causes:**

- 1) **Infection:** Streptococci, TB, Histoplasmosis, Brucellosis, Campylobacter.
- 2) **Systemic disease:** Sarcoidosis, IBD (UC/CD), Behcet's.
- 3) **Malignancy/lymphoma.**
- 4) **Drugs:** Penicillins, Sulphonamides, combined OCP.
- 5) **Pregnancy.**

- Apart from the chest x ray, the following are also important:

- A throat culture
- Antistreptolysin-O test (ASOT)
- Mantoux test

The commonest cause of EN is streptococcal infection.

EX: A 35-year-old female presents tender, erythematous nodules over her forearms with elevated serum calcium level >>>> think of sarcoidosis.

Pt with EN >>> the most useful next investigation is >>> **chest x-ray** as it helps exclude **sarcoidosis** and **tuberculosis**, the two most important cause of EN.

## **2) Pyoderma gangrenosum:**

- **Features:**

- Typically on the **lower limbs**.
- Initially **small red papule**.
- Later **deep, red, necrotic ulcers** with a **violaceous border**.
- May be accompanied systemic symptoms e.g. Fever, myalgia.

- **Causes\***

- 1) **Idiopathic** in **50%**, may also be seen in:
- 2) **GIT:**
  - **Inflammatory bowel disease:** ulcerative colitis, Crohn's.
  - **Primary sclerosing cholangitis**
  - **Primary biliary cirrhosis.**

3) **Connective tissue disorders:** RA and SLE.

4) **Haematological malignancy:**

- **Myeloproliferative disorders.**
- **Lymphoma, myeloid leukaemias.**
- **Monoclonal gammopathy (IgA).**

• Management:

- 1) The potential for **rapid progression is high** in most patients and most doctors advocate **oral steroids (prednisolone) as first-line treatment.**
- 2) Other immunosuppressive therapy, for example cyclosporine and infliximab, have a role in difficult cases.

Note whilst Pyoderma gangrenosum can occur in DM it is rare and is generally not included in a differential of potential causes.

**EX:** A 34-year-old man with a history of polyarthralgia, back pain and diarrhoea is found to have a 3 cm red lesion on his shin which is starting to ulcerate. What is the most likely diagnosis? >>> **Ulcerative colitis**, which has a known association with large-joint arthritis, sacroilitis and **Pyoderma gangrenosum**.

**3) Pretibial myxoedema:**

- Symmetrical, erythematous lesions seen in **Graves'** disease.
- **Shiny, orange peel** skin.

**4) Necrobiosis lipoidica diabetorum:**

- **Shiny, painless** areas of **yellow/red** skin on the shin of diabetics.
- Often associated with **telangiectasia**.

**Cellulitis**

Cellulitis is a term used to describe an inflammation of the skin and subcutaneous tissues, typically due to infection by Streptococcus pyogenes or Staphylococcus aureus.

**Features:**

- Commonly occurs on the **shins**.
- Erythema, pain, swelling.
- There may be some associated systemic upset such as fever.

**Management:**

- The BNF recommends **flucloxacillin** as **first-line** treatment for mild/moderate cellulitis.
- **Clarithromycin** or **clindamycin** is recommend in patients **allergic** to penicillin.
- Many local protocols now suggest the use of **oral clindamycin** in patients who have **failed to respond to flucloxacillin**.
- Severe cellulitis should be treated with **intravenous benzylpenicillin + flucloxacillin**.

**Malignant melanoma: prognostic factors**

The primary **risk factors** for melanoma includes:

- 1) Exposure to **ultraviolet** radiation (sun).
- 2) Geographic location in a **sunny climate located near the equator**.
- 3) **Fair** skinned individuals
- 4) Increasing age, particularly **men > 50 years**.
- 5) A personal or **family history** of a 1 st degree relative with melanoma.
- 6) **Dysplastic** naevi.
- 7) **Greater than 50 naevi 2 mm or more in diameter.**
- 8) **Xeroderma pigmentosum**
- 9) **Familial atypical mole melanoma syndrome.**

The **invasion depth** of a tumour (Breslow depth) is the single most important factor in determining prognosis of patients with malignant melanoma.

**Melanoma >>> the invasion depth of the tumour is the single most important prognostic factor**

Breslow Thickness	Approximate 5 year survival
< 1 mm	95-100%
1 - 2 mm	80-96%
2.1 - 4 mm	60-75%
> 4 mm	50%

### **Lentigo maligna**

Lentigo maligna is a type of melanoma in-situ.

It typically progresses slowly but may at some stage become invasive causing Lentigo maligna melanoma.

It is flat brown pigmentation with a jagged, irregular edge. The pigmentation on the anterior aspect of the lesion is a darker brown.

### **Venous ulceration**

Venous ulceration is typically **seen above the medial malleolus**.

Investigations:

- **Ankle-brachial pressure index (ABPI)** is important in **non-healing ulcers** to assess for poor arterial flow which could impair healing.
- An ankle-brachial pressure index measurement would help exclude arterial insufficiency as a contributing factor. If this was abnormal then a referral to the vascular surgeons should be considered.
- The ABPI readings indicate a reasonable arterial supply and suggest the ulcers are **venous in nature**.
- A '**normal**' ABPI may be regarded **as between 0.9 - 1.2**.
- **Values below 0.9 indicate arterial disease**.
- Interestingly, **values above 1.3 may also indicate arterial disease**, in the form of **false-negative results secondary to arterial calcification** (e.g. in **diabetics**).

Management:

- **Compression multi-layer bandaging**, usually 4 layer: it is the only treatment shown to be of real benefit, it reduce LL oedema and improve the chances of healing.
- It is also crucial for patients to rest and keep the leg up where possible.
- Oral pentoxifylline, a peripheral vasodilator, improves healing rate.
- Small evidence base supporting use of flavonoids
- Little evidence to suggest benefit from hydrocolloid dressings, topical growth factors, ultrasound therapy and intermittent pneumatic compression.

- If the ulcer fails to heal with active management (e.g. Compression bandaging) then referral for consideration of biopsy to exclude a malignancy should be made.

<b>Management of venous ulceration &gt; compression multi-layer bandaging</b>
---

<b>ABPI</b> measurement is essential before beginning bandaging, as if there is significant arterial insufficiency, blood supply to the limb may be threatened.
---

An ABPI of <b>0.8</b> has become a <b>pivotal figure</b> in the management of leg ulceration, defining the <b>cut-off point</b> for high compression banding and is frequently taken as indicating the presence of a so-called “ <b>mixed ulcer</b> ”.
--

### Scabies (see pic)

- Scabies is caused by the mite *Sarcoptes scabiei* and is spread by prolonged skin contact.
- It typically affects children and young adults.
- The scabies mite burrows into the skin, laying its eggs in the stratum corneum.
- The **intense pruritus** associated with scabies is due to a **delayed type IV hypersensitivity reaction** to mites/eggs which **occurs about 30 days after the initial infection**.

### Features:

- **Widespread pruritus**
- **Linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist**
- In infants the face and scalp may also be affected
- Secondary features are seen due to scratching: excoriation, infection

### Management:

- **Permethrin 5%** is **first-line**
- **Malathion 0.5%** is **second-line**
- Give appropriate guidance on use (see below)
- **Pruritus persists for up to 4-6 weeks post eradication**

### Patient guidance on treatment (from Clinical Knowledge Summaries):

- Avoid close physical contact with others until treatment is complete.
- **All household and close physical contacts should be treated at the same time, even if asymptomatic.**
- Launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

The BNF advises to apply the insecticide **to all areas**, including the **face** and **scalp**, contrary to the manufacturer's recommendation. Patients should be given the following instructions:

- Apply the insecticide cream or liquid to cool, dry skin.
- Pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow.
- **Allow to dry and leave on the skin for 8-12 hours for Permethrin, or for 24 hours for Malathion, before washing off.**
- Reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc.
- **Repeat treatment 7 days later.**

**Scabies >>> Permethrin treatment: all skin including scalp + leave for 12 hours + retreat in 7 days.**

### Crusted (Norwegian) scabies:

- Crusted scabies is seen in pt. with suppressed immunity, especially **HIV**.
- The crusted skin will be teeming with hundreds of thousands of organisms.
- **Ivermectin** is the treatment of choice and isolation is essential.

### **Pityriasis versicolor (see pic)**

Pityriasis versicolor, also called **tinea versicolor**, is a superficial cutaneous fungal infection caused by *Malassezia furfur* (formerly termed *Pityrosporum ovale*).

Features:

- Most commonly affects **trunk**
- **Patches** may be **hypo pigmented, pink or brown** (hence **versicolor**)
- **Scale** is common
- Mild pruritus

Predisposing factors:

- Occurs in **healthy** individuals
- Immunosuppression
- Malnutrition
- Cushing's

Management:

- 1) **Topical antifungal** e.g. **Terbinafine (Lamisil®)** or **selenium sulphide (Selsun blue ®)**.
- 2) **If extensive disease or failure** to respond to topical treatment then >> consider **oral Itraconazole**.



**Seborrhoeic dermatitis in adults** (see pic)

Seborrhoeic dermatitis in adults is a **chronic dermatitis** thought to be caused by an inflammatory reaction related to a proliferation of a normal skin inhabitant, a fungus called *Malassezia furfur* (formerly known as *Pityrosporum ovale*).

It is common, affecting around 2% of the general population.

Features:

- **Eczematous** lesions on the **sebum-rich areas**: **scalp** (may cause **dandruff**), periorbital, **auricular** and **nasolabial folds**.
- **Otitis externa** and **blepharitis** may develop.

The two complications that are most associated with seborrhoeic dermatitis are: **Otitis externa** and **blepharitis**.

Associated conditions include:

- 1) **HIV**
- 2) **Parkinson's disease**

Seborrhoeic dermatitis is more common in patients with Parkinson's disease and patients with HIV.

Scalp disease management:

- 1) **Over the counter** preparations containing **zinc** pyrithione ('Head & Shoulders') and **tar shampoo** ('Neutrogena T/Gel') are **first-line**.
- 2) The preferred **second-line** agent is **topical ketoconazole**.
- 3) **Selenium sulphide shampoo** and **topical corticosteroid** may also be useful.

Face and body management:

- Topical antifungals: e.g. Ketoconazole.
- Topical steroids: best used for short periods.
- Difficult to treat - **recurrences are common**.

There is less role for emollients / Aqueous cream in the management of seborrhoeic dermatitis than in other chronic skin disorders.

EX: A 67-year-old man with a history of Parkinson's disease presents due to the development of an itchy, red rash on his neck, behind his ears and around the nasolabial folds. He had a similar flare up last winter but did not seek medical attention. What is the most likely diagnosis? >> Seborrhoeic dermatitis.

**Acne rosacea (see pic)**

Acne rosacea is a **chronic skin disease** of **unknown** aetiology.

Features:

- Typically affects **nose, cheeks** and **forehead**
- **Flushing** is often first symptom
- **Telangiectasia** are common
- Later develops into **persistent erythema** with **papules** and **pustules**
- **Rhinophyma**
- Ocular involvement: blepharitis

Management:

- 1) **Topical metronidazole** may be used for mild symptoms (i.e. Limited number of papules and pustules, no plaques).
- 2) More severe disease >> **systemic antibiotics: oral Oxytetracycline.**
- 3) Recommend daily application of a high-factor **sunscreen.**
- 4) **Camouflage creams** may help conceal redness.
- 5) **Laser** therapy may be for patients with prominent telangiectasia.

Long-term use of **minocycline** ☹ in particular has been associated with **non-dose dependent blue-grey pigmentation** of skin in the lower legs, and mucosal pigmentation.

Oxytetracycline and doxycycline can lead to photosensitivity, but skin pigmentation seems to be specific to minocycline rather than a class effect of the tetracyclines.

**Pityriasis rosea (see Pic)**

Overview:

- Cause unknown, herpes hominis virus 7 (HHV-7) a possibility.
- Tends to affect **young adults.**

Features:

- **Herald patch** (usually on **trunk**).
- Followed by **erythematous, oval, flat scaly patches** which follow a **characteristic distribution** with the longitudinal diameters of the oval lesions **running parallel** to the line of Langer. This may produce a **'fir-tree' appearance.**

Management:

- Self-limiting, usually disappears after 4-6 weeks.

**Impetigo (see pic)**

Impetigo is a superficial bacterial skin infection usually caused by either ***Staphylococcus aureus*** or *Streptococcus pyogenes*.

Features:

- **'Golden', crusted** skin lesions **typically** found **around the mouth**.
- **Very contagious**.

**Management:**

Limited, localised disease:

- 1) **Topical Fusidic acid** is **first-line**.
- 2) **Topical retapamulin (Altabax ®)** is used **second-line** if fusidic acid has been ineffective or is not tolerated.
- 3) **If MRSA** is suspected; as in hospital stay and lack of response to fusidic acid; it is not susceptible to either fusidic acid or retapamulin, so **topical mupirocin (Bactroban®)** should therefore be used in this situation.

Extensive disease:

- Oral flucloxacillin
- Oral erythromycin if penicillin allergic

**Keratoacanthoma (see pic)**

Keratoacanthoma is a **benign epithelial** tumour.

They are more frequent in **middle age** and do not become more common in old age (unlike basal cell and squamous cell carcinoma).

Features - said to look like a **volcano** or **crater**:

- Initially a smooth dome-shaped papule.
- **Rapidly grows** to become a **crater centrally-filled with keratin**.

**Spontaneous** regression of Keratoacanthoma **within 3 months** is common, often resulting in a **scar**.

Whilst Keratoacanthoma is a benign lesion, such lesions should however be **urgently excised** as it is **difficult clinically to exclude squamous cell carcinoma**. Removal also may prevent scarring, so **urgent referral to the dermatologist**.

**Erythema ab igne (see pic)**

Erythema ab igne is a skin disorder caused by **over exposure to infrared radiation**. Characteristic features include **reticulated, erythematous patches** with **hyperpigmentation** and **telangiectasia**.

A typical history would be an **elderly women** who **always sits next to an open fire** (e.g. **Patient with Hypothyroidism can make patients feel cold and hence more likely to sit next a heater / fire**).

If the cause is not treated then patients may go on to develop squamous cell skin cancer.

### **Actinic keratosis (AK)** (see pic)

Actinic, or solar, keratosis (AK) is a **common premalignant skin lesion** that develops as a consequence of **chronic sun exposure**.

Features:

- **Small, crusty or scaly**, lesions.
- May be pink, red, brown or the same colour as the skin.
- Typically on sun-exposed areas e.g. **temples of head**.
- **Multiple** lesions may be present.

Management options include:

- 1) **Prevention** of further risk: e.g. sun avoidance, sun cream.
- 2) **Fluorouracil cream**: typically for a **2 to 3 week course**. The skin will become red and inflamed - sometimes **topical hydrocortisone is given following fluorouracil** to help settle the inflammation.
- 3) **Topical diclofenac**: may be used for mild AKs. Moderate efficacy but much fewer side-effects.
- 4) **Topical Imiquimod**: trials have shown good efficacy.
- 5) Cryotherapy.
- 6) Curettage and cautery.

**EX:** Old pt. with multiple number of erythematous, rough lesions on the back of her hands >>> **Actinic keratosis (AK) >>> Topical Fluorouracil cream.**

**EX** A 67-year-old man is diagnosed with actinic keratosis on his right temple and prescribed fluorouracil cream. One week later he presents as the skin where he is applying treatment has become red and sore. On examination there is no sign of weeping or blistering. What is the most appropriate action? >> This is a **normal reaction to treatment**. Fluorouracil should be continued for at least another week before starting topical steroids. So, **Continue fluorouracil cream + review in 1 week, NOT** (Continue fluorouracil cream + prescribe topical hydrocortisone to use concurrently).

**Genital warts**

- Genital warts (also known as **condylomata accuminata**) are a common cause of attendance at genitourinary clinics.
- They are caused by the many varieties of the human papilloma virus **HPV**, especially types **6 & 11**.
- It is now well established that HPV (primarily types 16,18 & 33) predisposes to cervical cancer.

Features:

- **Small** (2 - 5 mm) **fleshy protuberances** which are slightly pigmented.
- May bleed or itch

Management:

- **Topical podophyllum** or **cryotherapy** are commonly used as **first-line** treatments depending on the location and type of lesion.
- Multiple, non-keratinised warts are generally best treated with topical agents whereas solitary, keratinised warts respond better to cryotherapy.
- **Imiquimod** is a topical cream which is generally used **second** line.
- Genital warts are often resistant to treatment and recurrence is common although the majority of anogenital infections with HPV clear without intervention within 1-2 years.

**Dermatitis herpetiformis (see pic)**

Dermatitis herpetiformis is an **autoimmune blistering** skin disorder associated with **coeliac** disease. It is caused by **deposition** of **IgA** in the **dermis**.

Features:

- **Itchy, vesicular** skin lesions on **the extensor surfaces** (e.g. **elbows, knees, buttocks**).

Diagnosis:

- 1) **Skin biopsy**: direct **immunofluorescence** shows deposition of **IgA** in a granular pattern in the upper **dermis**.
- 2) **Anti-gliadin antibody**.

Management:

- 1) **Gluten-free diet**
- 2) **Dapsone**

### Herpes simplex virus (HSV)

There are two strains of the herpes simplex virus (HSV) in humans: HSV-1 and HSV-2. Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap.

The most common cause of multiple shallow ulcers in both heterosexual and homosexual males is **herpes simplex**.

Features:

- Primary infection: may present with a **severe gingivostomatitis**
- **Cold sores**
- **Painful genital ulceration**
- **Flu-like symptoms, inguinal lymphadenopathy and urethral discharge.**

Diagnosis: **PCR for herpes simplex.**

Management:

- Gingivostomatitis: **oral acyclovir**, chlorhexidine mouthwash.
- Cold sores: topical acyclovir although the evidence base for this is modest.
- Genital herpes: oral acyclovir.
- Some patients with frequent exacerbations may benefit from longer term acyclovir.

**EX:** A 23-year-old man presents with a three day history of general malaise and low-grade temperature. Yesterday he developed extensive painful ulceration of his mouth and gums. On examination his temperature is 37.4°C, pulse 84 / min and there is submandibular lymphadenopathy. What is the most likely diagnosis? >>> Gingivostomatitis, a characteristic feature of primary HSV infection.

### Onycholysis

Onycholysis describes **the separation of the nail plate from the nail bed.**

Causes:

- 1) Idiopathic
- 2) Trauma e.g. Excessive manicuring
- 3) Infection: especially fungal
- 4) Skin disease: psoriasis, dermatitis
- 5) Impaired peripheral circulation e.g. **Raynaud's**
- 6) Systemic disease: hyper- and hypothyroidism

**Keloid scars**

Keloid scars are **tumour-like lesions** that arise from the connective tissue of a scar and extend beyond the dimensions of the original wound.

Predisposing factors:

- Ethnicity: more common in people with **dark** skin
- Occur more commonly in **young adults(20-40 years)**, rare in the elderly
- Common sites (in order of decreasing frequency): **sternum**, shoulder, neck, face, extensor surface of limbs, trunk.

Keloid scars - more common in <b>young, black, male</b> adults.
---

Keloid scars are most common on the <b>sternum</b> .
--

Treatment:

- 1) **Early** keloids may be treated with **intra-lesional steroids** e.g. **triamcinolone**.
- 2) **Excision** is sometimes required.

Keloid scars are **less** likely if incisions are made along **relaxed** skin tension lines. Langer lines were historically used to determine the optimal incision line. They were based on procedures done on cadavers but have been shown to produce worse cosmetic results than when following skin tension lines.

**Vitiligo (see pic)**

Vitiligo is an **autoimmune** condition which results in the loss of melanocytes and consequent depigmentation of the skin.

It is thought to affect around **1%** of the population and symptoms typically develop by the age of **20-30 years**.

Features:

- **Well demarcated patches of depigmented skin.**
- The peripheries tend to be most affected.
- **Trauma may precipitate new lesions (Koebner phenomenon).**

Associated conditions:

- 1) **Pernicious anaemia (in 9%)**
- 2) **Type 1 DM (in 5.7%)**
- 3) **Autoimmune thyroid disorders** (as Hashimoto thyroiditis & Graves')
- 4) **Addison's disease**
- 5) **Polyglandular autoimmune syndrome**
- 6) **Alopecia areata**
- 7) **Rheumatoid arthritis,**
- 8) **Inflammatory bowel disease**
- 9) **Psoriasis.**

**NB:** **HLA-B13** appears to be the link between thyroid disease and vitiligo.

**NB:** 9% of patients with pernicious anaemia have been shown to have vitiligo, compared to 5.7% with DM.

Management:

- 1) Sun block for affected areas of skin.
- 2) Camouflage make-up.
- 3) Topical corticosteroids may reverse the changes if applied early.
- 4) There may also be a role for topical Tacrolimus and phototherapy, although caution needs to be exercised with light-skinned patients.

### **Hirsutism and hypertrichosis**

**Hirsutism** is often used to describe **androgen-dependent hair growth** in women, with **hypertrichosis** being used for **androgen-independent hair growth**.

**Polycystic ovarian syndrome** is the most common causes of **hirsutism**.

Other causes include:

- 1) **Cushing's syndrome**
- 2) **Congenital adrenal hyperplasia**
- 3) Androgen therapy
- 4) Obesity: due to peripheral conversion oestrogens to androgens
- 5) Adrenal tumour
- 6) Androgen secreting ovarian tumour
- 7) Drugs: **Phenytoin, Minoxidil, Cyclosporine, Diazoxide**

Assessment of hirsutism:

Ferriman-Gallwey scoring system: 9 body areas are assigned a score of 0 - 4, a score > 15 is considered to indicate moderate or severe hirsutism.

Management of hirsutism:

- Advise weight loss if overweight.
- Cosmetic techniques such as waxing/bleaching - not available on the NHS.
- Consider using **combined oral contraceptive pills** such as **co-cyprindiol (Dianette)** or ethinylestradiol and drospirenone (Yasmin). Co-cyprindiol should not be used long-term due to the increased risk of venous thromboembolism.
- Facial hirsutism: **topical eflornithine** - contraindicated in pregnancy and breast-feeding.



**Causes of hypertrichosis:**

- 1) Drugs: **Phenytoin, Minoxidil, Cyclosporine, Diazoxide**
- 2) **Congenital** hypertrichosis lanuginosa.
- 3) **Congenital** hypertrichosis terminalis.
- 4) **Porphyria cutanea tarda.**
- 5) **Anorexia nervosa.**

**Skin disorders associated with malignancy (see pic)**

Paraneoplastic syndromes associated with internal malignancies:

Skin disorder	Associated malignancies
<b>Acanthosis nigricans</b>	<b>GIT, Gastric</b> cancer
Acquired ichthyosis	Lymphoma
Acquired hypertrichosis lanuginosa	Gastrointestinal and lung cancer
<b>Dermatomyositis</b>	<b>Lung</b> and <b>Ovarian</b> cancer
<b>Erythema gyratum repens</b>	<b>Solid organ malignancies</b> such as <b>Lung</b> cancer & <b>Breast</b> cancer.
<b>Erythroderma</b>	<b>Lymphoma</b>
<b>Migratory thrombophlebitis</b>	<b>Pancreatic</b> cancer
<b>Necrolytic migratory erythema</b>	<b>Glucagonoma</b>
<b>Pyoderma gangrenosum</b> (bullous and non-bullous forms)	<b>Myeloproliferative disorders</b>
<b>Sweet's syndrome</b> (also known as acute febrile neutrophilic dermatosis)	Haematological malignancy e.g. <b>Myelodysplasia, AML</b> - tender, purple plaques
<b>Tylosis</b>	<b>Oesophageal</b> cancer

### **Erythroderma**

Erythroderma is a term used when **more than 95%** of the skin is involved in a **rash** of **any** kind.

Causes of Erythroderma:

- 1) **Eczema**
- 2) **Psoriasis** (Erythrodermic psoriasis).
- 3) Drugs e.g. **gold**
- 4) **Lymphoma, leukaemia**
- 5) **Idiopathic**

- Erythroderma is an **emergency** as patients are susceptible to **profound dehydration, infection and hypothermia**.
- **Methotrexate tab** would be the only correct treatment for someone with erythrodermic psoriasis.
- Steroids could lead to unstable pustular psoriasis and would not generally work.
- Hydroxychloroquine has little effect on psoriasis.
- Topical coal tar and Dithranol are good treatments for chronic plaque psoriasis but are highly irritant and would make the erythroderma much more inflamed and deteriorate his condition.

### **Eczema: diagnosis**

#### **UK Working Party Diagnostic Criteria for Atopic Eczema:-**

An **itchy skin** condition in the last 12 months **Plus** three or more of:

- 1) **Onset below age 2 years** (not used in children under 4 years).
- 2) History of **flexural involvement** or dermatitis on the cheeks and/or extensor areas in children aged 18 months or under.
- 3) **Visible flexural dermatitis**
- 4) History of generally **dry skin**.
- 5) Personal history of **other atopic disease** in children aged under 4 years, history of atopic disease in a first degree relative may be included.

**Cyclosporine** is a well-used drug in the treatment of **atopic dermatitis (AD)**. It is usually at doses of 2-5 mg/kg.

The pathophysiology of AD is complex but the **T lymphocytes** are involved and it is known that there is an increased production of cytokines particularly **IL-4**.

Cyclosporine is a suppressor of T cells and in that respect works very well in atopic dermatitis and psoriasis.

The side effects of hypertension and renal toxicity limit its use.

**Eczema herpeticum**

Eczema herpeticum describes a **severe primary** infection of the **skin** by herpes simplex virus **HSV** 1 or 2.

It is more commonly seen in **children with atopic eczema**.

As it is **potentially life threatening** children should be **admitted** for **IV acyclovir**.

**EX:** A 9-year-old child with a history of atopic eczema presents with a sudden worsening of her skin. Her eczema is usually well controlled with emollients but her parents are concerned as the facial eczema has got significantly worse overnight. She now has painful clustered blisters on both cheeks, around her mouth on her neck. Her temperature is 37.9°C. >>> **Eczema herpeticum >>> hospitalization and IV Acyclovir**.

**Pompholyx (see pic)**

Pompholyx is a type of **eczema** which affects both the **hands** (**cheiropompholyx**) and the **feet** (**pedopompholyx**).

It is also known as dyshidrotic eczema or vesicular eczema.

Features:

- Small **blisters** on the **palms** and **soles**.
- **Pruritic**, sometimes burning sensation.
- Once blisters burst skin may become dry and crack.

Management:

- 1) Cool compresses
- 2) Emollients
- 3) Topical steroids

## Eczema: topical steroids

Use weakest steroid cream which controls patient's symptoms.

The table below shows topical steroids by potency:

Mild	Moderate	Potent	Very potent
<b>Hydrocortisone</b> 0.5-2.5%	<b>Betamethasone</b> valerate 0.025% ( <b>Betnovate RD®</b> )  <b>Clobetasone</b> <u>butyrate</u> 0.05% ( <b>Eumovate</b> )	<b>Fluticasone</b> propionate 0.05% ( <b>Cutivate®</b> )  Betamethasone valerate 0.1% (Betnovate)	<b>Clobetasol</b> <u>propionate</u> 0.05% ( <b>Dermovate®</b> )

Topical steroids:

- Moderate: Clobetasone butyrate 0.05%
- Potent: Betamethasone valerate 0.1%
- Very potent: Clobetasol propionate 0.05%

Finger tip rule: 1 finger tip unit (FTU) = 0.5 g, sufficient to treat a skin area about twice that of the flat of an adult hand.

Topical steroid doses for eczema in adults:

Area of skin	Fingertip units per dose
Hand and fingers (front and back)	1.0
A foot (all over)	2.0
Front of chest and abdomen	7.0
Back and buttocks	7.0
Face and neck	2.5
An entire arm and hand	4.0
An entire leg and foot	8.0

The BNF makes recommendation on the quantity of topical steroids that should be prescribed for an adult for a single daily application for 2 weeks:

Area	Amount
Face and neck	15 to 30 g
Both hands	15 to 30 g
Scalp	15 to 30 g
Both arms	30 to 60 g
Both legs	100 g
Trunk	100 g
Groin and genitalia	15 to 30 g

### **Acanthosis nigricans (see pic)**

Describes **symmetrical, brown, velvety plaques** that are often found on the **neck, axilla** and **groin**.

Causes:

- 1) **Gastrointestinal cancer**
- 2) **DM**
- 3) Obesity
- 4) Polycystic ovarian syndrome
- 5) Acromegaly
- 6) Cushing's disease
- 7) **Hypothyroidism**
- 8) Familial
- 9) Prader-Willi syndrome
- 10) Drugs: oral contraceptive pill, nicotinic acid

## **Hypersensitivity**

The **Gell and Coombs classification** divides hypersensitivity reactions into 4 types:

### **Type I – Anaphylactic:**

- Antigen reacts with IgE bound to mast cells.
- EX: Anaphylaxis, atopy (e.g. asthma, eczema and hay fever).

### **Type II - Cell bound:**

- IgG or IgM binds to antigen on cell surface.
- EX: Autoimmune haemolytic anaemia, **ITP**, Goodpasture's, pernicious anemia, acute hemolytic transfusion reactions, rheumatic fever, bullous Pemphigoid, pemphigus vulgaris.

### **Type III - Immune complex:**

- Free antigen and antibody (IgG, IgA) combine.
- Serum sickness, SLE, post-streptococcal glomerulonephritis, extrinsic allergic alveolitis (especially acute phase).

### **Type IV - Delayed hypersensitivity:**

- T cell mediated.
- Tuberculosis, tuberculin skin reaction, graft versus host disease (GVHD), allergic contact dermatitis, **scabies**, extrinsic allergic alveolitis (especially chronic phase), multiple sclerosis, Guillain-Barre syndrome.

In recent times a further category has been added:

### **Type V:**

- Antibodies that recognise and bind to the cell surface receptors, either stimulating them or blocking ligand binding.
- **Graves'** disease, myasthenia **gravis**.

A 15-year-old girl presents with an urticarial rash, angioedema and wheezing. Her mother states that she has just come from her younger sister's party where she had been helping to blow up balloons. What is the most likely diagnosis? >> This is a typical history of **latex allergy**. **Adrenaline** should be given immediately and usual anaphylaxis management followed.

## Allergy tests

<b>Skin prick test</b>	<p>Most commonly used test as <b>easy</b> to perform and <b>inexpensive</b>.</p> <p>Drops of diluted allergen are placed on the skin after which the skin is pierced using a needle.</p> <p>A large number of allergens can be tested in one session.</p> <p>Normally includes a <b>histamine (positive)</b> and <b>sterile water (negative) control</b>.</p> <p>A wheal will typically develop if a patient has an allergy. Can be interpreted after <b>15 minutes</b>.</p> <p>Useful for <b>food allergies</b> and also <b>pollen</b>.</p>
<b>Radioallergosorbent test (RAST)</b>	<p>Determines the <b>amount of IgE</b> that reacts specifically with suspected or known allergens, for example IgE to egg protein.</p> <p>Results are given in grades from 0 (negative) to 6 (strongly positive).</p> <p>Useful for <b>food allergies</b>, <b>inhaled</b> allergens (e.g. Pollen) and <b>wasp/bee venom</b>. لدغة دبور / نحلة</p> <p>Blood tests may be used when skin prick tests are not suitable, for example if there is extensive eczema or if the patient is taking antihistamines.</p>
<b><u>Skin patch testing:</u></b>	<p>Useful for <b>contact dermatitis</b>.</p> <p>Around 30-40 allergens are placed on the back.</p> <p><b>Irritants</b> may also be tested for not just <b>allergens</b>.</p> <p>The patches are removed <b>48 hours later</b> with the results being read by a dermatologist <b>after a further 48 hours</b>.</p>

### Contact dermatitis

There are two main types of contact dermatitis:

- **Allergic contact dermatitis: type IV hypersensitivity reaction. Uncommon** - often seen on the **head following hair dyes**. Presents as an acute weeping eczema which predominately affects **the margins of the hairline rather than the hairy scalp itself**. **Topical** treatment with a **potent steroid** is indicated.

**Nickel dermatitis** is a **common cause allergic contact dermatitis** and is an example of a type **IV** hypersensitivity reaction. It is often caused by **jewellery** such as **watches**. It is diagnosed by a **skin patch test**.

Cement is a frequent cause of contact dermatitis. The alkaline nature of cement may cause an irritant contact dermatitis whilst the dichromates in cement also can cause an allergic contact dermatitis.

- **Irritant contact dermatitis: common** - non-allergic reaction due to weak acids or alkalis (e.g. **detergents**). Often seen on the **hands**. Erythema is typical, crusting and vesicles are rare.

### Latex allergy

Sensitivity to latex may cause a number of problems:

- Type I hypersensitivity (anaphylaxis)
- Type IV hypersensitivity (allergic contact dermatitis)
- Irritant contact dermatitis

Latex allergy is more common in children with myelomeningocele spina bifida.

#### **Latex-fruit syndrome:**

It is recognised that many people who are allergic to latex are also allergic to fruits, particularly **banana, pineapple, avocado, chestnut, kiwi fruit, mango**, passion fruit and **strawberry**.

**EX:** A nurse who is known to have an allergy to latex develops a widespread urticarial rash and facial oedema shortly after eating lunch. Which food is she most likely to have consumed >> **Latex-fruit syndrome**.

### Erythema multiforme (EM) (see pic)

Features:

- **Target lesions.**
- Initially seen on the **back of the hands / feet** before spreading to the torso.
- **Upper limbs** are more commonly affected than the lower limbs.
- Pruritus is occasionally seen and is usually mild.



If symptoms are severe and involve blistering and mucosal involvement the term **Stevens-Johnson syndrome** is used.

Causes:

- Viruses: **HSV (the most common cause)** about **50% of cases**, Orf (Orf is a skin disease of sheep and goats caused by a parapox virus).
- Idiopathic.
- Bacteria: Mycoplasma, Streptococcus.
- Drugs: **Penicillin V**, **Sulphonamides**, **Carbamazepine**, **Allopurinol**, **NSAIDs**, **Oral contraceptive pill**, Nevirapine.
- Connective tissue disease e.g. SLE.
- **Sarcoidosis**.
- **Malignancy: leukaemia, lymphoma**

### Stevens-Johnson syndrome (SJS)

Stevens-Johnson syndrome is the **severe** form of **erythema multiforme** associated with **mucosal** involvement and **systemic** symptoms.

Features:

- 1) **Rash** is typically **maculopapular** with **target lesions** being characteristic. May develop into vesicles or bullae.
- 2) **Mucosal** involvement.
- 3) **Systemic** symptoms: fever, arthralgia.

Causes:

- Same like the causes of **Erythema multiforme (EM)**.

The antibiotic which is most associated with the development of Stevens-Johnson syndrome is >>> **Sulphonamides (Co-trimoxazole)**.

### Toxic epidermal necrolysis (TEN)

TEN is a **potentially life-threatening skin disorder** that is most commonly seen secondary to an **idiosyncratic drug reaction**.

It is a severe **mucocutaneous exfoliative** disease with an **uncertain** pathogenesis and a **high mortality rate**.

Patients present with **erythematous-to-dusky** plaques and **targetoid** lesions that progress rapidly to **painful, full-thickness**, epidermal desquamation involving **more than 30% of body surface area (face, trunk & limbs)**. **Mucosal** involvement is also seen.

In this condition the skin develops a **scalded** appearance over an **extensive area**. Some authors consider TEN to be **the severe end of a spectrum** of skin disorders which includes **erythema multiforme** and **Stevens-Johnson syndrome**.

Features:

- Systemically unwell e.g. **pyrexia**, tachycardia
- **Diffuse** erythematous, **painful rash** with evidence of some lateral sliding of these erythematous areas on palpation.
- **Positive Nikolsky's sign: the epidermis separates with mild lateral pressure.**

Causes:

- 1) **Viral** infections.
- 2) **Leukaemia** and **lymphoma**.
- 3) **Drugs** known to induce TEN:
  - 1) **Phenytoin**
  - 2) **Carbamazepine**
  - 3) **Penicillins**
  - 4) **Sulphonamides**
  - 5) **Allopurinol**
  - 6) **NSAIDs**

Management:

- 1) **Stop** precipitating factor.
- 2) Supportive care, often in ICU.
- 3) **IVIG** Intravenous immunoglobulin has been shown to be effective and is now commonly used **first-line**.
- 4) Other treatment options include: immunosuppressive agents (cyclosporine and cyclophosphamide), Plasmapheresis.

## **Alopecia**

Alopecia may be divided into scarring (destruction of hair follicle) and non-scarring (preservation of hair follicle).

### **Scarring alopecia:**

- 1) Trauma, burns
- 2) Radiotherapy
- 3) Lichen planus
- 4) Discoid lupus
- 5) Tinea capitis (scarring may develop in untreated tinea capitis if a kerion develops).

### **Non-scarring alopecia:**

- 1) Male-pattern baldness.
- 2) Drugs: cytotoxic drugs, **Carbimazole**, **Colchicine**, **Heparin (Anti-Coagulant)**, **oral Contraceptive pill**.
- 3) Nutritional: iron and zinc deficiency.
- 4) Autoimmune: alopecia areata.
- 5) **Telogen effluvium** (hair loss following stressful period e.g. surgery).
- 6) **Trichotillomania**.

**Alopecia areata**

- Alopecia areata is a presumed **autoimmune** condition causing **localised, well demarcated** patches of hair loss.
- At the edge of the hair loss, there may be small, broken 'exclamation mark' hairs.
- Hair will regrow in 50% of patients by 1 year, and in 80-90% eventually.
- **Watchful waiting** for **spontaneous remission** and **careful explanation** is therefore sufficient in many patients.
- Neither the British Association of Dermatologists nor Clinical Knowledge Summaries recommend screening for autoimmune disease.
- **Other** treatment options include:
  - **Topical or intralesional corticosteroids (triamcinolone).**
  - Topical Minoxidil.
  - Phototherapy.
  - Dithranol.
  - Contact immunotherapy.
  - Wigs.

**EX:** Young female with IDDM e' alopecia areata >> Intra-lesional triamcinolone

**Skin disorders associated with diabetes**

Note whilst Pyoderma gangrenosum can occur in DM it is rare and is often not included in a differential of potential causes.

**1) Necrobiosis lipoidica diabetorum:** (see pic)

- Shiny, **painless** areas of yellow/red/brown skin typically on the shin.
- Often associated with surrounding telangiectasia.
- It is seen in 0.3-1% of patients with DM.
- The exact cause of necrobiosis lipoidica is unknown, but the leading theory of necrobiosis lipoidica has focused on diabetic microangiopathy.
- Around 40-60% of patients with Necrobiosis lipoidica have DM and the condition may pre-date the development of abnormal blood sugar.
- More common in females.
- Biopsy: granuloma formation with infiltration of lymphocytes, plasma cells and eosinophils.
- TTT: **Topical / injectable steroids**, skin grafting ± camouflage creams.

**2) Granuloma annulare:** (see pic)

- **Papular** lesions that are often **slightly hyperpigmented** and **depressed centrally**.
- Typically occur on the **dorsal** surfaces of the **hands and feet**, and on the extensor aspects of the arms and legs (**shin**).

- It is not clear from recent studies if there is actually a significant association between DM and granuloma annulare, but it is often listed in major textbooks.

### 3) Infection:

- Candidiasis
- Staphylococcal

### 4) Neuropathic ulcers

### 5) Vitiligo

### 6) Lipoatrophy

## Skin disorders associated with tuberculosis

Possible skin disorders:

- 1) **Lupus vulgaris** (accounts for **50%** of cases) (see pic)
- 2) **Erythema nodosum**
- 3) **Scarring alopecia**
- 4) **Scrofuloderma**: breakdown of skin overlying a tuberculous focus
- 5) **Verrucosa cutis**
- 6) **Gumma**

Lupus vulgaris is the most common form of cutaneous TB seen in the Indian subcontinent. It generally occurs on the face and is common around the nose and mouth. The initial lesion is an **erythematous flat plaque** which gradually becomes **elevated** and may **ulcerate** later.

## Pruritus

The most important causes of pruritus:

- 1) **Iron deficiency anaemia.**
- 2) **Polycythaemia.**
- 3) **Liver disease.**
- 4) **Chronic kidney disease.**
- 5) **Lymphoma.**

Other causes:

- 1) **Hyper- and hypothyroidism**
- 2) **DM**
- 3) **Pregnancy**
- 4) **'Senile' pruritus**
- 5) **Urticaria**
- 6) **Skin disorders: eczema, scabies, psoriasis, Pityriasis rosea**

### **Zinc deficiency**

Features:

- **Perioral dermatitis:** red, crusted lesions around the corner of the mouth and below the lower lip.
- Acrodermatitis
- Alopecia
- Short stature
- Hypogonadism
- Hepatosplenomegaly
- Geophagia (ingesting clay/soil)
- Cognitive impairment

### **Acne vulgaris**

Acne vulgaris is a common skin disorder which usually occurs in **adolescence**. It typically affects the face, neck and upper trunk and is characterised by the **obstruction of the pilosebaceous follicle** with keratin plugs which results in **comedones** and **pustules**.

Epidemiology:

- Affects around **80-90% of teenagers**, 60% of whom seek medical advice.
- Acne may also persist beyond adolescence, **Acne is actually more common in females after the age of 25 years**, with **10-15% of females** and 5% of males over 25 years old being affected.

Pathophysiology is multifactorial:

- **Follicular epidermal hyperproliferation** resulting in the formation of a keratin plug. This in turn causes obstruction of the pilosebaceous follicle. Activity of sebaceous glands may be controlled by androgen, although levels are often normal in patients with acne.
- Colonisation by the **anaerobic** bacterium **Propionibacterium acnes**.
- Inflammation.

Acne may be classified into mild, moderate or severe:

- Mild: open and closed comedones with or without sparse inflammatory lesions.
- Moderate acne: widespread non-inflammatory lesions and numerous papules and pustules.
- Severe acne: extensive inflammatory lesions, which may include nodules, pitting, and scarring.

A simple step-up management scheme often used in the treatment of acne is as follows:

- 1) Washing the face using a mild soap with lukewarm water twice a day.
- 2) Single topical therapy (**topical Retinoids** and **benzyl peroxide**).
- 3) Combination topical therapy (as above+ **Topical antibiotic**).
- 4) Oral antibiotics:
  - E.g. **Oxytetracycline, doxycycline**. Improvement may not be seen for 3-4 months.
  - Minocycline is now considered less appropriate due to the possibility of irreversible skin pigmentation.
  - **Gram negative folliculitis** may occur as a **complication** of **long-term antibiotic** use - high-dose **oral trimethoprim** is effective if this occurs.
- 5) **Oral Isotretinoin**: only under supervision, used in **severe** acne.
- 6) **Ethinylestradiol + Cyproterone acetate (Dianette 35)** is useful in some female patients with acne unresponsive to standard treatment.

**Oral Erythromycin** may be used for **acne in pregnancy**. The other drugs are contraindicated.

**There is no role for dietary modification in patients with acne.**

### Isotretinoin

Isotretinoin is an **oral retinoid** used in the treatment of **severe acne**.

Two-thirds of patients have a long term remission or cure following a course of oral Isotretinoin.

Adverse effects:

- 1) **Teratogenicity: females** should ideally be using **two forms** of contraception (e.g. combined oral contraceptive pill and condoms).
- 2) **Dry skin, eyes and lips: the most common side-effect of Isotretinoin.**
- 3) Photosensitivity.
- 4) Nose bleeds (caused by dryness of the nasal mucosa).
- 5) Hair thinning.
- 6) Low mood.
- 7) **Raised triglycerides.**
- 8) **Benign intracranial hypertension**: Isotretinoin treatment should not be combined with tetracyclines for this reason.

**Isotretinoin >>> the most common side-effect is dry skin**

**Psoriasis** (see pic)

Psoriasis is a common (prevalence around 2%) and chronic skin disorder.

It generally presents with red, scaly patches on the skin although it is now recognised that patients with psoriasis are at increased risk of arthritis and cardiovascular disease.

Pathophysiology:

- Multifactorial and not yet fully understood
- Genetic: associated HLA-B13, -B17, and -Cw6. Strong concordance (70%) in identical twins.
- Immunological: **abnormal T cell activity** stimulates **keratinocyte proliferation**. There is increasing evidence this may be mediated by a novel group of T helper cells producing IL-17, designated Th17. These cells seem to be a third T-effector cell subset in addition to **Th1** and Th2. (**Psoriasis is mediated by type 1 helper T cells** which are involved in **the cell mediated response**, rather than type 2 helper T cells).
- Environmental: it is recognised that psoriasis may be worsened (e.g. Skin trauma, stress), triggered (e.g. Streptococcal infection) or improved (e.g. Sunlight) by environmental factors.

Recognised subtypes of psoriasis:

- 1) **Plaque psoriasis**: the **most common** sub-type resulting in the typical well demarcated red, scaly patches affecting the **extensor** surfaces, sacrum and scalp. **Scalp psoriasis may occur in isolation in patients with no history of psoriasis elsewhere.**
- 2) **Flexural psoriasis**: in contrast to plaque psoriasis the skin is smooth.
- 3) **Guttate psoriasis**: transient psoriatic rash frequently triggered by a streptococcal infection. Multiple red, teardrop lesions appear on the body.
- 4) **Pustular psoriasis**: commonly occurs on the palms and soles.
- 5) **Erythrodermic psoriasis**:
  - May result from progression of chronic disease to an **exfoliative** phase with plaques covering **most** of the body. Associated with mild systemic upset.
  - More serious form is an acute deterioration. This may be triggered by a variety of factors such as withdrawal of systemic steroids. Patients need to be admitted to hospital for management.

Other features:

- **Nail signs: pitting, Onycholysis**
- **Arthritis**

Complications:

- 1) **Psoriatic arthropathy** (around **10%**): **Psoriatic arthropathy may occur prior to the development of skin lesions.**
- 2) Increased incidence of metabolic syndrome
- 3) Increased incidence of cardiovascular disease
- 4) Increased incidence of venous thromboembolism
- 5) Psychological distress

### **Psoriasis: management**

NICE released guidelines on the management of psoriasis and psoriatic arthropathy.

#### **Chronic plaque psoriasis:**

- 1) Regular emollients may help to reduce scale loss and reduce pruritus.
- 2) **First-line:** NICE recommend a **potent corticosteroid applied once daily** plus **vitamin D analogue (Calcipotriol) applied once daily** (applied separately, one in the morning and the other in the evening) **for up to 4 weeks** as **initial** treatment.
- 3) **Second-line:** if no improvement after 8 weeks then offer a vitamin D analogue twice daily.
- 4) **Third-line:** if no improvement after 8-12 weeks then offer either: a potent corticosteroid applied twice daily for up to 4 weeks or a **coal tar** preparation applied once or twice daily.
- 5) Short-acting **dithranol** can also be used.

1 <sup>st</sup> line ttt of psoriatic <b>plaques</b> is >> <b>Topical steroid + topical Calcipotriol</b>
--

#### **Scalp psoriasis:**

- NICE recommend the use of **potent topical corticosteroids** used once daily for 4 weeks.
- If no improvement after 4 weeks then either use **a different formulation** of the potent corticosteroid (for example, a shampoo or mousse) and/or a **topical agents to remove adherent scale (for example, agents containing salicylic acid, emollients and oils)** before application of the potent corticosteroid.

#### **Face, flexural and genital psoriasis:**

- NICE recommend offering a mild or moderate potency corticosteroid applied once or twice daily for a maximum of 2 weeks.
- Topical Calcipotriol is usually irritant in flexures.
- Mild tar preparations are an option but may be messy and cumbersome.

<b>Flexural psoriasis &gt;&gt;&gt; topical steroid</b>
--



**Steroids in psoriasis:**

- **Topical steroids** are commonly used in **flexural** psoriasis and there is also a role for mild steroids in facial psoriasis.
- If steroids are ineffective for these conditions **vitamin D analogues** or **Tacrolimus ointment** should be used second line.
- Pts. should have **4 week breaks between** courses of topical steroids.
- **Very potent steroids should not be used for longer than 4 weeks** at a time. **Potent steroids can be used for up to 8 weeks at a time.**
- The scalp, face and flexures are particularly prone to steroid atrophy so topical steroids should not be used for more than 1-2 weeks/month

**Secondary care management:****1) Phototherapy:**

- **Narrow band ultraviolet B light** is now the treatment of choice. If possible this should be given 3 times a week.
- **Photo-chemotherapy** is also used - **Psoralens + Ultraviolet A light (PUVA).**
- Adverse effects: skin ageing, **squamous cell cancer (NOT melanoma).**

**2) Systemic therapy:**

- 1) **Oral methotrexate** is used **first**-line. It is particularly useful if there is associated joint disease.
- 2) **Cyclosporine.**
- 3) **Systemic Retinoids.**
- 4) **Biological** agents: infliximab, etanercept and adalimumab.
- 5) **Ustekinumab** (IL-12 and IL-23 blocker) is showing promise in early trials.

**Mechanism of action of commonly used drugs:**

- **Coal tar:** probably inhibit DNA synthesis. It is smelly and messy - most patients would not tolerate facial application.
- **Calcipotriol:** vitamin D analogue which reduces epidermal proliferation and restores a normal horny layer. Calcipotriol is not recommended for facial lesions as it may cause irritation - calcitriol and tacalcitol are alternatives.
- **Dithranol:** inhibits DNA synthesis, wash off after 30 mins, SE: burning, staining.

**The following factors may exacerbate psoriasis:**

- 1) **Trauma.**
- 2) **Alcohol.**
- 3) **Drugs:** (Reactions may occur from less than 1 month to 1 year after the medication is initiated):
  - **Beta blockers,**
  - **ACEIs,**
  - **Lithium,**
  - **Antimalarials** (chloroquine and hydroxychloroquine) and
  - **NSAIDs.**
- 4) **Withdrawal of systemic steroids.**

**NB:** Precipitation of the rash may take **up to a year to develop after** initiation of the medications.

**NB:** It is still difficult to establish the link between anti-malarial and psoriasis exacerbation.

**NB:** Lithium prescription with ACEI is not recommended due to the problem of a significant increase in serum Lithium levels.

**NB:** The **safest** treatment - that which produces the best clinical effect with minimal side effects >>> Psoralen and ultraviolet light (**PUVA**).

**NB:** **Oral steroids are contraindicated in psoriasis** and although one may see an initial improvement, a very serious rebound effect may be seen.

### Psoriasis: guttate (see pic)

**Guttate psoriasis** is more common in **children and adolescents**.

It may be precipitated by a **streptococcal** infection (sore throat/tonsillitis) **2-4 weeks prior** to the lesions appearing.

Features:

- **Tear drop papules** on the **trunk and limbs** which in parts are covered by a **fine scale**.

Management:

- Most cases resolve **spontaneously** within 2-3 months
- There is **no** firm evidence to support the use of antibiotics to eradicate streptococcal infection.
- Topical agents as per psoriasis
- UVB phototherapy
- Tonsillectomy may be necessary with recurrent episodes

### Koebner phenomenon

The Koebner phenomenon describes **skin lesions** which **appear at the site of injury**. It is seen in:

- 1) **Psoriasis**
- 2) **Vitiligo**
- 3) **Warts**
- 4) **Lichen planus**
- 5) **Lichen sclerosus**
- 6) **Molluscum contagiosum**

### Porphyria cutanea tarda

Porphyria cutanea tarda is **the most common hepatic porphyria**.

It is due to an inherited defect in uroporphyrinogen decarboxylase or caused by hepatocyte damage e.g. alcohol, hepatitis C, oestrogens.

Features:

- 1) Classically presents with **photosensitive rash** with **blistering** and skin **fragility (extremely fragile and tears easily)** on the **face** and **dorsal aspect of hands** (most common feature).
- 2) **Hypertrichosis**.
- 3) **Hyperpigmentation**.

Porphyria cutanea tarda:

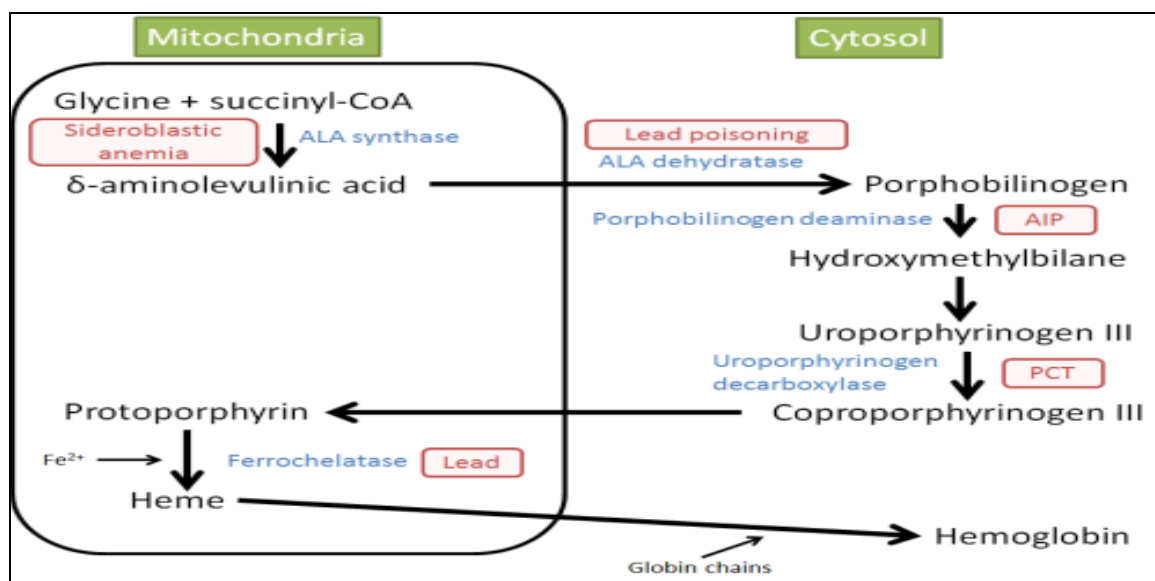
- 1) Blistering photosensitive rash
- 2) Hypertrichosis
- 3) Hyperpigmentation

Investigations:

- Urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp.

Management:

- Chloroquine
- Venesection



### Pemphigus vulgaris (see pic)

Pemphigus vulgaris is an **autoimmune** disease caused by **antibodies** directed against **desmoglein 3**, a cadherin-type epithelial cell adhesion molecule. It is more common in the Ashkenazi Jewish population.

**Blisters/bullae:**

- No mucosal involvement (in exams at least) >>> **Bullous Pemphigoid**
- Mucosal involvement >>> **Pemphigus vulgaris**

**Features:**

- **Mucosal ulceration** is common and often the presenting symptom. **Oral** involvement is seen in 50-70% of patients.
- **Skin blistering - flaccid, easily ruptured** vesicles and bullae. Lesions are typically **painful** but **not itchy**. These may develop months after the initial mucosal symptoms. Nikolsky's describes the spread of bullae following application of horizontal, tangential pressure to the skin.
- Acantholysis on biopsy.

**Management:**

- Steroids.
- Immunosuppressants.

**Bullous Pemphigoid (see pic)**

- Bullous Pemphigoid is an **autoimmune** condition causing **sub-epidermal blistering** of the skin.
- This is secondary to the development of **antibodies** against **hemidesmosomal proteins BP180 and BP230**.
- Bullous Pemphigoid is more common in **elderly** patients.

**Features:**

- **Itchy, tense blisters** typically around flexures.
- The blisters usually **heal without scarring**
- **Mouth is usually spared**.

In reality around 10-50% of patients have a degree of mucosal involvement. It would however be unusual for an exam question to mention mucosal involvement as it is seen as a classic differentiating feature between Pemphigoid and Pemphigus.

**Skin biopsy:**

**Immunofluorescence** shows **IgG** and **C3** at the **dermoepidermal** junction.

**Management:**

- Referral to dermatologist for biopsy and confirmation of diagnosis.
- **Oral corticosteroids** are the mainstay of treatment.
- Topical steroids, immunosuppressants and antibiotics are also used.

### **Systemic mastocytosis**

Systemic mastocytosis results from **a neoplastic proliferation of mast cells**.

Features:

- 1) **Urticaria pigmentosa** - produces a wheal on rubbing (Darier's sign).
- 2) **Flushing**.
- 3) **Abdominal pain**.
- 4) **Monocytosis** on the blood film.

Diagnosis:

- **↑ Serum tryptase levels.**
- **↑ Urinary histamine.**

**EX:** A 17-year-old man presents with a 2 week history of abdominal pain, diarrhoea and repeated episodes of flushing. Examination reveals urticarial skin lesions on the trunk. >>> **Systemic mastocytosis** >>> **↑ Urinary histamine.**

NB:

- Given the history of diarrhoea and flushing a diagnosis of **carcinoid syndrome** should be considered, which would be investigated with **urinary 5-HIAA levels**. This would not however explain the urticarial skin lesions.
- **In a young person a diagnosis of systemic mastocytosis should be considered.**
- Another factor against carcinoid syndrome is the age of the patient - the average **age** of a patient with a **carcinoid** tumour is **61** years.

### **Fungal nail infections (Onychomycosis)**

**Onychomycosis** is fungal infection of the nails. This may be caused by:

- 1) **Dermatophytes** - mainly **Trichophyton rubrum**, accounts for **90%** of cases.
- 2) Yeasts - such as Candida.
- 3) Non-Dermatophytes moulds.

Features:

- **'Unightly' nails** are a **common reason for presentation**.
- **Thickened, rough, opaque nails** are the most common **finding**.

Investigation:

- **Nail clippings**
- **Scrapings** of the affected nail

Management:

- Treatment is successful in around **50-80%** of people.
- **Diagnosis should be confirmed by microbiology before starting ttt.**
- **Dermatophytes** infection: **Oral Terbinafine (Lamisil ®)** is currently recommended **first**-line with oral itraconazole as an alternative.
  - **6 weeks - 3 months** therapy is needed for **fingernail** infections.
  - Whilst **toenails** should be treated for **3 - 6 months**.
- Candida infection: mild disease should be treated with topical antifungals (e.g. Amorolfine) whilst more severe infections should be treated with oral itraconazole for a period of 12 weeks.

**EX:** Pt with type **1 DM** presents with **unsightly toenails** affecting the lateral three nails of the left foot. On examination the nails are brown and break easily. **Nail scrapings** demonstrate **Trichophyton rubrum** infection.  
>>> TTT **Oral Terbinafine for 3 – 6 months.**

## **Tinea**

Tinea is a term given to Dermatophytes fungal infections.

Three main types of infection are described depending on what part of the body is infected:

- 1) Tinea **capitis** - scalp
- 2) Tinea **corporis** - trunk, legs or arms
- 3) Tinea **pedis** - feet

### **Tinea capitis (scalp ringworm):**

- A cause of **scarring alopecia** mainly seen in **children**.
- If untreated a raised, pustular, spongy/boggy mass called a **kerion** may form.
- Most common cause is **Trichophyton tonsurans** in the UK and the USA.
- May also be caused by **Microsporum canis** acquired from cats or dogs.
- Diagnosis:
  - The most useful investigation is **scalp scrapings**.
  - Lesions due to *Microsporum canis* green fluorescence under Wood's lamp.
  - Lesions due to *Trichophyton* species do not readily fluoresce under Wood's lamp.
- Management (based on CKS guidelines):
  - **Oral antifungals:**
    - **Terbinafine** for *Trichophyton tonsurans* infections and
    - **Griseofulvin** for *Microsporum* infections.
  - **Topical ketoconazole shampoo** should be given for **the first two weeks** to reduce transmission.

### Tinea corporis:

- Causes include **Trichophyton rubrum** and **Trichophyton verrucosum** (e.g. from contact with cattle).
- Well-defined annular, erythematous lesions with pustules and papules.
- May be treated with **oral fluconazole**.

### Tinea pedis (athlete's foot):

- Characterised by itchy, peeling skin between the toes.
- Common in adolescence.

### **Myxoid cyst (mucous cysts)** (see pic)

They are **benign ganglion cysts** usually found on the **distal, dorsal** aspect of the **finger**. It is firm dome-shaped swelling. There is usually **osteoarthritis** in the surrounding joint. They are more common in **middle-aged women**.

### **Molluscum contagiosum** (see pic)

Molluscum contagiosum is caused by a **pox virus (DNA)** infection.

It is typically seen in **younger children** and results in **characteristic small, pearly, umbilicated (central dimple)** lesions.

Molluscum contagiosum is **highly infectious**.

Lesions **may be present for up to 12 months** and usually **resolve spontaneously**. Whilst various treatments may be effective in removing the lesions (e.g. surgery, cryotherapy, topical agents) **no treatment is recommend** in the **initial** phase due to the benign nature of the condition.

### **Hyperhidrosis**

Hyperhidrosis describes the **excessive production of sweat**.

Management options include:

- 1) **Topical aluminium chloride** preparations are **first-line**. Main side effect is skin irritation.
- 2) Iontophoresis: particularly useful for patients with palmar, plantar and axillary hyperhidrosis.
- 3) Botulinum toxin: currently licensed for axillary symptoms.
- 4) Surgery: e.g. endoscopic transthoracic sympathectomy. Patients should be made aware of the risk of compensatory sweating.

### **Otitis externa**

Otitis externa is a common reason for primary care attendance in the UK.

Causes of otitis externa include:

- 1) Infection: bacterial (Staphylococcus aureus, Pseudomonas aeruginosa) or fungal.
- 2) Seborrhoeic dermatitis.
- 3) Contact dermatitis (allergic and irritant).

Features:

- Ear pain, itch, discharge.
- Otoscopy: red, swollen, or eczematous canal.

The recommend initial management of otitis externa is:

- **Topical antibiotic or a combined topical antibiotic with steroid.**
- **If the tympanic membrane is perforated aminoglycosides** are traditionally **not** used, **but** many ENT doctors **disagree** with this and feel that concerns about ototoxicity are unfounded.
- **If there is canal debris** then consider **removal**.
- If the canal is extensively swollen then an ear wick is sometimes inserted.

Second line options include:

- Consider contact dermatitis secondary to neomycin.
- Oral antibiotics if the infection is spreading.
- Taking a swab inside the ear canal.
- Empirical use of an antifungal agent.

**Malignant otitis externa** is more common in **elderly diabetics**. In this condition there is extension of infection into the **bony** ear canal and the soft tissues deep to the bony canal. **Intravenous antibiotics** may be required.

### **Erythrasma (see pic)**

Erythrasma is a generally **asymptomatic, well-demarcated**, flat, slightly scaly, pink or brown **macular rash** usually found in the **groin** or **axillae**.

It is caused by an overgrowth of the **diphtheroid Corynebacterium minutissimum**.

Examination with **Wood's light fluorescence** reveals a coral-red fluorescence.

**Topical miconazole or antibacterial** are usually effective. Oral erythromycin may be used for more extensive infection.

### **Photosensitive skin disorders**

Diseases aggravated by exposure to sunlight:

- 1) **SLE, discoid lupus.**
- 2) **Porphyria cutanea tarda** (NOT acute intermittent Porphyria).
- 3) **Herpes labialis** (cold sores).
- 4) **Pellagra.**
- 5) **Xeroderma pigmentosum.**
- 6) Solar urticaria.
- 7) Polymorphic light eruption.



### **Yellow nail syndrome**

Slowing of the nail growth leads to the characteristic thickened and discoloured nails seen in yellow nail syndrome.

Associations:

- 1) **Congenital lymphoedema**
- 2) **Pleural effusions**
- 3) **Bronchiectasis**
- 4) **Chronic sinus infections**

### **Café-au-lait spots**

Hyperpigmented lesions that vary in colour from light brown to dark brown, with borders that may be smooth or irregular.

Causes:

- 1) **Neurofibromatosis** type I & II
- 2) **Tuberous sclerosis**
- 3) **Fanconi anaemia**
- 4) **McCune-Albright syndrome**

### **Pellagra (see pic)**

Pellagra is caused by **nicotinic acid (niacin) deficiency**.

The classical features are the **3 D's** - **Dermatitis**, **Diarrhoea** and **Dementia**.

Pellagra may occur as a consequence of **isoniazid therapy** (isoniazid inhibits the conversion of tryptophan to niacin) and it is more common in **alcoholics**.

Features:

- 1) **Dermatitis** (red-brown, symmetrically scaly rash on sun-exposed sites - termed Casal's necklace if around neck).
- 2) **Diarrhoea**.
- 3) **Dementia**, depression.
- 4) **Death** if not treated.

### **Parvovirus B19**

Parvovirus B19 is a **DNA** virus which causes a variety of clinical presentations.

It was identified in the **1980's** as the cause of **erythema infectiosum**.

Erythema infectiosum (also known as **fifth disease** or '**slapped-cheek syndrome**):

- Most common presenting illness.
- Systemic symptoms: lethargy, fever, headache.
- 'Slapped-cheek' rash spreading to proximal arms and extensor surfaces.

Other presentations:

- Asymptomatic.
- **Pancytopenia** in immunosuppressed patients.
- **Aplastic crises** e.g. **in sickle-cell disease** (parvovirus B19 suppresses erythropoiesis for about a week so aplastic anaemia is rare unless there is a chronic haemolytic anaemia).

### **Bullous disorders**

Causes of skin bullae:

- 1) Congenital: **epidermolysis bullosa**
- 2) Autoimmune: **bullous Pemphigoid, pemphigus**
- 3) **Insect bite**
- 4) **Trauma/friction**
- 5) Drugs: **barbiturates, furosemide**

### **Discoid lupus erythematosus**

Discoid lupus erythematosus is a benign disorder generally seen in **younger females**. It very rarely progresses to SLE (in less than 5% of cases).

It is characterised by **follicular keratin plugs** and is thought to be **autoimmune** in aetiology.

Features:

- **Erythematous, raised rash**, sometimes **scaly**
- May be photosensitive
- More common on **face**, neck, ears and **scalp**
- Lesions heal with atrophy, **scarring** (may cause **scarring alopecia**), and pigmentation.

Management:

- 1) **Topical steroid**.
- 2) **Oral antimalarials** may be used **second-line** e.g. **hydroxychloroquine**
- 3) Avoid sun exposure

TTT Discoid lupus erythematosus: 1) topical steroids → 2) oral hydroxychloroquine
---

### **Polycystic ovarian syndrome (PCOS): management**

PCOS is a complex condition of ovarian dysfunction thought to affect between **5-20%** of women of **reproductive age**.

Management is complicated and problem based partly because the aetiology of PCOS is not fully understood.

Both **hyperinsulinaemia** and **high levels of LH** are seen in PCOS and there appears to be some overlap with the **metabolic syndrome**.

General:

- 1) **Weight reduction** if appropriate
- 2) If a women requires contraception then a **combined oral contraceptive (COC)** pill may help regulate her cycle and induce a monthly bleed.

Hirsutism and acne:

- 1) A **COC** pill may be used help manage hirsutism.
- 2) Possible options include a third generation COC which has fewer androgenic effects or **co-cyprindiol (Cyproterone acetate + Ethinylestradiol) (Diane 35 ®)** which **has an anti-androgen action**. Both of these types of COC may carry an increased risk of venous thromboembolism.
- 3) **If** doesn't respond to COC >>> then **topical eflornithine (Vaniqa cream® 1x2)** may be tried.
- 4) **Spiroinolactone, finasteride (Proscar ®5 mg 1x1)** and **flutamide** may be used under specialist supervision.

Infertility:

- Weight reduction if appropriate
- The management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether **clomifene, metformin** or a combination should be used to stimulate ovulation.
- A 2007 trial published in the New England Journal of Medicine suggested **clomifene was the most effective treatment**. There is a potential risk of **multiple pregnancies** with anti-oestrogen therapies such as clomifene because it work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion.
- The RCOG published an opinion paper in 2008 and concluded that on current evidence **metformin is not a first line treatment of choice in the management of PCOS**
- Metformin is also used, either combined with clomifene or alone, particularly in patients who are obese.
- **Gonadotrophins**.

## **Leprosy**

Leprosy is a **granulomatous** disease primarily affecting the **peripheral nerves** and **skin**. It is caused by **Mycobacterium leprae**.

Features:

- Patches of **hypopigmented** skin typically affecting the **buttocks, face, and extensor surfaces of limbs**.
- **Sensory loss**.

The degree of **cell mediated immunity** determines the type of leprosy a patient will develop.

**Low** degree of cell mediated immunity → **lepromatous** leprosy ('**multibacillary**')

- **Extensive** skin involvement.
- **Symmetrical** nerve involvement.

High degree of cell mediated immunity → tuberculoid leprosy ('**paucibacillary**')

- Limited skin disease.
- Asymmetric nerve involvement.

Management:

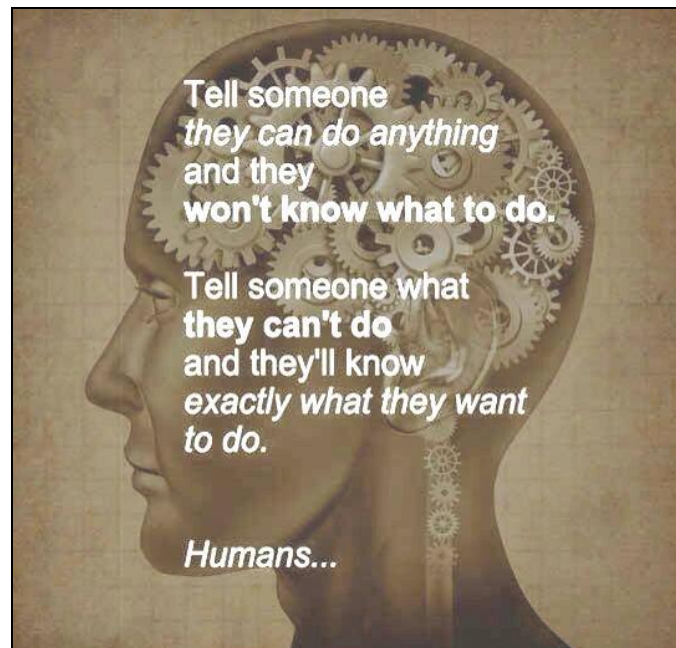
WHO-recommended **triple therapy**: Rifampicin+ Dapsone +Clofazimine.

## **Drugs causing photosensitivity**

Causes of drug-induced photosensitivity:

- 1) **Amiodarone**
- 2) **Thiazides**
- 3) **Sulphonylureas**
- 4) **Sulphonamides, Ciprofloxacin, Tetracyclines**
- 5) **NSAIDs** e.g. piroxicam
- 6) **Psoralens** (oral ttt of vitiligo)

# Clinical Sciences & Biostatistics & Miscellaneous



Screening test statistics

The available data should be used to construct a contingency table as below:

**TP** = true positive; **FP** = false positive; **TN** = true negative; **FN** = false negative

	Disease present	Disease absent
Test positive	TP	FP
Test negative	FN	TN

The table below lists the main statistical terms used with screening tests:

Measure	Formula	Plain English
<b>Sensitivity</b>	$TP / (TP + FN)$	Proportion of patients <b>with</b> the condition who have a <b>positive</b> test result.
<b>Specificity</b>	$TN / (TN + FP)$	Proportion of patients <b>without</b> the condition who have a <b>negative</b> test result.
<b>Positive predictive value (PPV)</b>	$TP / (TP + FP)$	The chance that the patient <b>has</b> the condition if the diagnostic test is <b>positive</b>
<b>Negative predictive value (NPV)</b>	$TN / (TN + FN)$	The chance that the patient does <b>not</b> have the condition if the diagnostic test is <b>negative</b>
<b>Likelihood ratio for a <u>positive</u> test result</b>	$\text{sensitivity} / (1 - \text{specificity})$	How much the odds of the disease increase when a test is positive
<b>Likelihood ratio for a <u>negative</u> test result</b>	$(1 - \text{sensitivity}) / \text{specificity}$	How much the odds of the disease decrease when a test is negative

Positive and negative predictive values are prevalence dependent.

Likelihood ratios are not prevalence dependent.

**Increasing** the cut-off of a **positive** test result will **decrease** the number of **false positives** and hence increase the specificity.

**EX:** A new test to screen for pulmonary embolism (PE) is used in 100 patients who present to the Emergency Department. The test is positive in 30 of the 40 patients who are proven to have a PE. Of the remaining 60 patients, only 5 have a positive test. What is the sensitivity of the new test?

A contingency table can be constructed from the above data, as shown below:

	PE diagnosed	NO PE
Test positive	30	5
Test negative	10	55

The sensitivity =  $TP / (TP + FN)$

The sensitivity is therefore  $30 / (30 + 10) = 75\%$

**EX:** A new blood test is developed to screen for prostate cancer. Trials have shown it has a **sensitivity** for detecting clinically significant prostate cancer of **80%** but a **specificity** of **60%**.

What is the likelihood ratio for a positive test result?

Likelihood ratio for a positive test result =  $\text{sensitivity} / (1 - \text{specificity})$

=  $0.8 / (1 - 0.6) = 2$

#### **Screening: Wilson and Junger criteria**

1. The condition should be **an important** public health problem.
2. There should be **an acceptable treatment for** patients with recognised disease.
3. **Facilities** for diagnosis and treatment should be available.
4. There should be **a recognised latent or early symptomatic stage**.
5. The natural **history** of the condition, including its development from latent to declared disease should be adequately understood.
6. There should be a suitable **test** or examination.

7. The test or examination should be **acceptable** to the population
  8. There should be **agreed policy** on whom to treat.
  9. The **cost** of case-finding (including diagnosis and subsequent treatment of patients) should be economically balanced in relation to the possible expenditure as a whole.
  10. **Case-finding** should be a continuous process and not a 'once and for all' project.
- N.B: NOT** The condition should be potentially curable.

### Study design

The following table highlights the main features of the main types of study:

Study type	Key features
<b>Randomised controlled trial (RCT)</b>	<p>Participants randomly allocated to intervention or control group (e.g. standard treatment or placebo).</p> <p>RCT is the gold standard for evaluation of efficacy for therapeutic and preventative measures.</p> <p>Practical or ethical problems may limit use.</p>
<b>Cohort study</b>	<p><b>Observational and prospective.</b></p> <p>Two (or more) are selected according to their exposure to a particular agent (e.g. medicine, toxin) and followed up to see how many develop a disease or other outcome.</p> <p>The usual outcome measure is <b>relative risk (RR)</b>.</p> <p>Examples include “<b>Framingham Heart Study</b>”</p> <div><p><b>EX:</b> A cohort study is being designed to look at the relationship between <b>smoking</b> and <b>breast cancer</b>. The usual outcome measure in a cohort study is the <b>relative risk</b>.</p></div>



Study type	Key features
<b>Case-control study</b>	<p>Observational and <b>retrospective</b>.</p> <p>Patients with a particular condition (cases) are identified and matched with (controls).</p> <p>Data is then collected on past exposure to a possible causal agent for the condition.</p> <p>The usual outcome measure is the <b>odds ratio</b>.</p> <p><b>Inexpensive</b>, produce <b>quick</b> results.</p> <p>Useful for studying <b>rare conditions</b>.</p> <p>Prone to confounding</p> <p>EX: to assess whether living near electricity pylons is a risk factor for childhood leukaemia.</p>
<b>Cross-sectional survey</b>	<p>Provide a 'snapshot', sometimes called <b>prevalence</b> studies.</p> <p>Provide <b>weak</b> evidence of cause and effect.</p>

A new antihypertensive drug needs to be investigated to establish its relative **potency**. Which of technique is most appropriate for this purpose >> **Bioassay** (Biological assays)

In a test of **efficacy** of an antihypertensive drug >> **a double blind, randomised** design would be favourable.

### Intention to treat analysis

Intention to treat analysis is a method of analysis for randomized controlled trials (RCT) in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment.

Intention to treat analysis is done to **avoid** the effects of **crossover** and **drop-out**, which may affect the randomization to the treatment groups, so **include the patients who drop out in the final data set**.

In RCT >>> **include the patients who drop out in the final data set**.

### Study design: new drugs

When a new drug is launched there are a number of options available in terms of study design.

One option is a **placebo controlled trial**. Whilst this may provide robust evidence it may be considered **unethical** if established treatments are available and it also does **not provide a comparison with standard treatments**.

If a drug is therefore to be compared to an existing treatment a statistician will need to decide whether the trial is intended to show superiority, equivalence or non-inferiority:

- **Superiority:** whilst this may seem the natural aim of a trial one problem is the **large sample size needed** to show a significant benefit over an existing treatment.
- **Equivalence:** an **equivalence margin is defined (-delta to +delta)** on a specified outcome. If the confidence interval of the difference between the two drugs **lies within the equivalence margin** then the drugs may be assumed to have a similar effect.
- **Non-inferiority:** similar to equivalence trials, but only the lower confidence interval needs to lie within the equivalence margin (i.e. -delta). **Small sample sizes are needed** for these trials. Once a drug has been shown to be non-inferior large studies may be performed to show superiority.

It should be remembered that drug companies may not necessarily want to show superiority over an existing product. If it can be demonstrated that their product is equivalent or even non-inferior then they may compete on price or convenience.

**EX:** A new oral-hypoglycaemic is being developed. A number of different study types are considered to demonstrate efficacy in reducing the HbA1c. Which study designs would require the most patients to produce a significant result >>> **Superiority trial**.

### Significance tests: types

The type of significance test used depends on whether the data is **parametric** (something which can be **measured**, usually **normally distributed**) or non-parametric.

#### Parametric tests:

- 1) **Student's t-test - paired or unpaired.**
- 2) **Pearson's product-moment coefficient - correlation**

**Non-parametric tests:**

- 1) **Mann-Whitney U test** - unpaired data.
- 2) **Wilcoxon signed-rank test** - compares **two sets** of observations on a **single** sample.
- 3) **Chi-squared test**: used to compare proportions or **percentages**.
- 4) **Spearman, Kendall rank – correlation**.

**Paired** data refers to data obtained from a **single** group of patients, e.g. Measurement before and after an intervention.

**Unpaired** data comes from **two different groups** of patients, e.g. Comparing response to different interventions in two groups.

**To test Correlation:**

- **Parametric** (normally distributed) >>> **Pearson's** coefficient.
- **Non-parametric** >>> **Spearman's** coefficient.

**EX:** A study measures a patient's serum cholesterol before and after a new lipid-lowering therapy has been given. What type of significance test should be used to analyse the data? >>> **Student's paired t-test**.

**EX:** A study is designed to assess the efficacy of a new anti-hypertensive medication. **Two groups** of patients are **randomly** assigned, one to take the established drug for 3 months whilst the other takes the new drug for 3 months. Blood pressure is measured before and after the intervention. There is then a **period off medication** for 1 month. After this period has **elapsed the medication that the groups receive is swapped around** and again blood pressure is measured before and 3 months later. The difference in blood pressure after the respective medications is calculated for each patient. Which one of the significance tests is it most appropriate to apply?

This describes a **crossover study**. As we are comparing **parametric** data from the **same patients** (they swapped medication halfway through the study) the **Student's paired t-test** should be used.

A clinical trial is conducted to study the benefits of a new oral medication to improve the symptoms of patients with COPD. In the trial 300 patients with COPD are given the new medication and a further 300 COPD patients are given a placebo.

Three months later they are asked to rate their symptoms using the following scale: *much improved, slight improvement, no change, slight worsening, significantly worse*.

What is the most appropriate statistical test to see whether the new medication is beneficial? >>> **Mann-Whitney U test**

**EX:** A study is designed on 50 persons to look at the efficacy of a mandible advancement device in reducing snoring. The severity of snoring was assessed by the partner using a 10 point scale **before** and **after** using the device. >>> **Wilcoxon signed-rank test**.

### Correlation and linear regression

Two measurements, or variables, may be plotted on a scatter plot.

For example, a study is performed to assess the correlation between age and systolic blood pressure. Age may be marked along the x axis and systolic blood pressure along the y axis.

#### Correlation:

The **correlation coefficient** (sometimes referred to as **Pearson's product-moment coefficient**) indicates how closely the points lie to a line drawn through the plotted data.

It is denoted by the **value r** which may lie **anywhere between -1 and 1**.

For example:

- **r = 1** - **strong positive** correlation (e.g. systolic blood pressure always increases with age).
- **r = 0** - **no** correlation (e.g. there is no correlation between systolic blood pressure and age).
- **r = - 1** - **strong negative** correlation (e.g. systolic blood pressure always decreases with age).

Whilst correlation coefficients give information about how one variable may increase or decrease as another variable increases they **do not give information about how much the variable will change**.

They also **do not provide** information on **cause** and **effect**.

It **can't be** used to **predict** systolic blood pressure for a given age.

### **Linear regression:**

In contrast to the correlation coefficient, linear regression may be used to **predict how much one variable changes when a second variable is changed.**

A regression equation may be formed,  $y = a + bx$ , where

- $y$  = the variable being calculated
- $a$  = the intercept value, when  $x = 0$
- $b$  = the slope of the line or regression coefficient. Simply put, how much  $y$  changes for a given change in  $x$
- $x$  = the second variable

### **Significance tests**

A null hypothesis ( $H_0$ ) states that two treatments are equally effective (and is hence negatively phrased).

A significance test uses the sample data to assess **how likely the null hypothesis is to be correct.**

For example:

- 'there is no difference in the prevalence of colorectal cancer in patients taking low-dose aspirin compared to those who are not'

The alternative hypothesis ( $H_1$ ) is the opposite of the null hypothesis, i.e. there is a difference between the two treatments.

The **p value** is **the probability of obtaining a result by chance at least as extreme** as the one that was actually observed, **assuming that the null hypothesis is true.** It is therefore equal to the chance of making a type I error (see below).

### **Two types of errors may occur when testing the null hypothesis:**

- **Type I:** the **null hypothesis is rejected when it is true** - i.e. Showing a difference between two groups when it doesn't exist, a false positive. This is determined against a preset significance level (termed alpha). As the significance level is determined in advance the chance of making a type I error is not affected by sample size. It is however increased if the number of end-points are increased. For example if a study has 20 end-points it is likely one of these will be reached, just by chance.
- **Type II:** the **null hypothesis is accepted when it is false** - i.e. failing to spot a difference when one really exists, a false negative. The probability of making a type II error is termed beta. It is determined by both sample size and alpha.

	Study accepts $H_0$	Study rejects $H_0$
Reality $H_0$		Type 1 error (alpha)
Reality $H_1$	Type 2 error (beta)	Power (1 - beta)

The **power of a study** is the probability of (correctly) **rejecting the null hypothesis when it is false**, i.e. the probability of detecting a statistically significant difference.

- **Power = 1 - the probability of making a type II error.**
- Power can be increased by **increasing the sample size**.

**The power of a study may be defined in a number of ways:**

- 1) In general terms, the probability that a **statistically significant difference** will be detected.
- 2) Probability of (correctly) **rejecting the null hypothesis** when it is **false**.
- 3) Which also means the probability of **confirming the alternative hypothesis** when **the alternative hypothesis is true**.
- 4) **Power = 1 - the probability of a type II error** or  $1 - \beta$ .

The significance level of a test is defined as the probability of rejecting the null hypothesis when the null hypothesis is actually true (a Type I error). It is often represented by the Greek symbol alpha.

A study is only statistically significant if the p-value reaches the significance level set before the study is started. Popular levels of significance are **5% (0.05)**, **1% (0.01)** and **0.1% (0.001)**.

### Odds and odds ratio

**Odds** are a ratio of the **number of people who incur a particular outcome** to the **number of people who do not incur the outcome**.

The **odds ratio** may be defined as the ratio of the odds of a particular outcome with experimental treatment and that of control.

**Odds** - remember a ratio of the number of people who **incur** a particular outcome to the number of people who **do not incur** the outcome. **NOT** a ratio of the number of people who **incur** a particular outcome to the **total** number of people.

**Odds vs. probability:**

In contrast, probability is the fraction of times you'd expect to see an event in many trials.

When expressed as a single number probability is always between 0 and 1. So, if we take the example of rolling a dice:

- The probability of rolling a six is  $1/6$  or 0.166666
- The odds of rolling a six is  $1/5$  or 0.2

**Odds ratios** are the usual reported measure in **case-control** studies.

It **approximates** to **relative risk** if the **outcome of interest is rare**.

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results:

	Total number of patients	Achieved = 50% pain relief
Paracetamol	60	40
Placebo	90	30

The **odds** of achieving significant pain **relief** with **paracetamol** =  $40 / 20 = 2$ .

The **odds** of achieving significant pain **relief** with **placebo** =  $30 / 60 = 0.5$ .

Therefore the **odds ratio** =  $2 / 0.5 = 4$

**EX:** A study looks at whether golf actually increases the risk of medial epicondylitis. Sixty people who regularly play golf are matched to sixty people who do not play golf. Thirty of the golfers had developed medial epicondylitis at some point compared to ten of the non-golfers.

What is the odds ratio of developing medial epicondylitis for people who play golf?

**Odds** of a golfer developing medial epicondylitis =  $30 / 30 = 1$ .

**Odds** a non-golfer developing medial epicondylitis =  $10 / 50 = 0.2$ .

The **odds ratio** is therefore =  $1 / 0.2 = 5$ .

### Relative risk (RR)

**Relative risk (RR)** is the ratio of risk in the experimental group (experimental event rate, EER) to risk in the control group (control event rate, CER).

The term relative risk ratio is sometimes used instead of relative risk.

It is the usual outcome measure of **cohort** studies.

To recap:

- EER = rate at which events occur in the experimental group
- CER = rate at which events occur in the control group

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results:

	Total number of patients	Experienced significant pain relief
Paracetamol	100	60
Placebo	80	20

**Experimental event rate, EER** =  $60 / 100 = 0.6$

**Control event rate, CER** =  $20 / 80 = 0.25$

Therefore the **relative risk ratio** =  $EER / CER = 0.6 / 0.25 = 2.4$

**If the risk ratio is > 1** then the rate of an event (in this case experiencing significant pain relief) is increased compared to controls.

It is therefore appropriate to calculate the **relative risk increase (RRI)** if necessary (see below).

**If the risk ratio is < 1** then the rate of an event is decreased compared to controls. The **relative risk reduction (RRR)** should therefore be calculated (see below).

**Relative risk increase (RRI)** or **Relative risk reduction (RRR)** is calculated by **dividing** the **absolute risk** change by the **control** event rate.

Using the above data,  $RRI = (EER - CER) / CER = (0.6 - 0.25) / 0.25 = 1.4 = 140\%$

Remember that **risk** and **odds** are different:



If 20 patients die out of every 100 who have a myocardial infarction then the **risk** of dying is  $20 / 100 = 0.2$  whereas the **odds** are  $20 / 80 = 0.25$ .

### Numbers needed to treat (NNT) and absolute risk reduction (ARR)

Numbers needed to treat (NNT) is a measure that indicates **how many patients** would require an intervention to reduce the expected number of outcomes by **one**.

EX: Results demonstrate that number needed to treat (**NNT**) is **20** for the prevention of the primary end-point.

This prevention study for stroke reveals that **20 patients need to be treated to prevent one event**.

Thus if you treat a **1000** patients then you will expect to have **50** fewer strokes.

It is calculated by  $1 / (\text{Absolute risk reduction})$  and is rounded to the next highest whole number.

$$\text{NNT} = 1 / \text{Absolute Risk Reduction (ARR)}$$

**Experimental event rate (EER)** = (Number who had particular outcome with the intervention) / (Total number who had the intervention).

**Control event rate (CER)** = (Number who had particular outcome with the control / (Total number who had the control).

$$\text{Absolute risk reduction (ARR)} = \text{CER} - \text{EER} \text{ or } \text{EER} - \text{CER}?$$

The absolute risk reduction (ARR) may be calculated by finding the absolute difference between the control event rate (CER) and the experimental event rate (EER).

You will often find both versions of the above listed in different sources.

In some ways it doesn't matter which you use as you will end up with the same answer but from a technical point of view:

- If the outcome of the study is **undesirable** then  $\text{ARR} = \text{CER} - \text{EER}$
- If the outcome of the study is **desirable** then  $\text{ARR}^* = \text{EER} - \text{CER}$

\*This may be more accurately termed absolute benefit increase, rather than absolute risk reduction

**EX:** A study is carried out to assess the potential of hip protectors to reduce femoral neck fractures in elderly nursing home patients. The average age of the patients was 82 years. Over a two-year period 800 patients were recruited and assigned randomly either to the hip protector group or standard care group.

**The results:**

Hip protector group: **400** patients - **10** of whom had a femoral neck fracture over the two year period.

Control group: **400** patients - **20** of whom had a femoral neck fracture over the two year period.

What is the absolute risk reduction?

The absolute risk reduction (ARR) = CER-EER, where:

$$\text{CER} = 20 / 400 = 1 / 20 = 0.05$$

$$\text{EER} = 10 / 400 = 1 / 40 = 0.025$$

$$\text{ARR} = \text{CER} - \text{EER} = 0.05 - 0.025 = 0.025$$

**EX:** A study is designed to assess a new proton pump inhibitor (PPI) in elderly patients who are taking aspirin. The new PPI is given to 120 patients whilst a control group of 240 is given the standard PPI. Over a five year period 24 of the group receiving the new PPI had an upper GI bleed compared to 60 who received the standard PPI. What is the absolute risk reduction?

Absolute risk reduction = (Control event rate) - (Experimental event rate).

$$(\text{ARR}) = \text{CER} - \text{EER}$$

$$\text{Control event rate} = 60 / 240 = 0.25$$

$$\text{Experimental event rate} = 24 / 120 = 0.2$$

$$\text{Absolute risk reduction} = 0.25 - 0.2 = 0.05 = 5\% \text{ reduction}$$

**EX:** A new drug is trialled for the treatment of lung cancer. Drug A is given to **500** people with early stage non-small cell lung cancer and a placebo is given to **450** people with the same condition. After 5 years **300** people who received drug A had survived compared to **225** who received the placebo.

What is the number needed to treat to save one life?

The question asks about the number needed to treat to **save one life**. The 'event' is therefore **survival**.

Experimental (drug A) event rate (**EER**) =  $300 / 500 = 0.6$

Control (placebo) event rate (**CER**) =  $225 / 450 = 0.5$

Absolute risk reduction (**ARR**) =  $0.6 - 0.5 = 0.1$

Number needed to treat (**NNT**) =  $1 / 0.1 = 10$

**EX:** A study looks at the benefits of adding a new antiplatelet drug to aspirin following a myocardial infarction. The following results are obtained:

Percentage of patients having further MI within 3 months was **4%** of patients treated with aspirin only, while was **3%** with patients treated with aspirin + the new drug.

What is the number needed to treat to prevent one patient having a further myocardial infarction within 3 months?

$NNT = 1 / \text{Absolute Risk Reduction.}$

$NNT = 1 / (\text{control event rate} - \text{experimental event rate}).$

$= 1 / (0.04 - 0.03) = 1 / (0.01) = 100$

**EX:** A **randomised controlled trial** is performed to look at a new drug to prevent hip fractures in postmenopausal women. Group A consists of 1,000 women who take the new drug whilst group B contains 1,400 women taking a placebo. The hip fracture rate in group A is 2% and in group B is 4%.

What is the number needed to treat to prevent one hip fracture?

The key to answering this question is to ignore irrelevant data such as the number of patients in each group.

Control event rate (**CER**) =  $4\% = 0.04$

Experimental event rate (**EER**) =  $2\% = 0.02$

Absolute risk reduction (**ARR**) =  $0.04 - 0.02 = 0.02$

$NNT = 1 / \text{Absolute Risk Reduction.}$

Number needed to treat (**NNT**) =  $1 / 0.02 = 50.$

**Hazard ratio (HR)**

The hazard ratio (HR) is **similar to relative risk** but is used when risk is not constant to time. It is typically used when **analysing survival over time**.

EX: A study is performed comparing **two chemotherapy regimens** for patients with small cell lung cancer. The end point of the study is **survival time**.

**Incidence and prevalence**

These two terms are used to describe the **frequency** of a condition in a population.

The **incidence** is the number of **new** cases per population in a given time **period**.

For example, if condition X has caused 40 new cases over the past 12 months per 1,000 of the population the annual incidence is 0.04 or 4%.

The **prevalence** is the **total** number of cases per population at **a particular point in time**. دلوقتى

For example, imagine a questionnaire is sent to 2,500 adults asking them how much they weigh. If from this sample population of 500 of the adults were obese then the prevalence of obesity would be 0.2 or 20%.

Relationship:

- **Prevalence = incidence \* duration of condition**
- In **chronic** diseases the **prevalence** is much greater than the incidence
- In **acute** diseases **the prevalence and incidence are similar**. For conditions such as the common cold the incidence may be greater than the prevalence.

**Pre- and post- test odds and probability****Pre-test probability:**

The proportion of people with the target disorder in the population at risk at a specific time (point **prevalence**) or time interval (period **prevalence**).

For example, the prevalence of rheumatoid arthritis in the UK is 1%

**Post-test probability:**

The proportion of patients with that particular test result who have the target disorder

Post-test probability = post-test odds / (1 + post-test odds)

**Pre-test odds:**

The odds that the patient has the target disorder before the test is carried out

Pre-test odds = pre-test probability / (1 - pre-test probability)

**Post-test odds:**

The odds that the patient has the target disorder after the test is carried out

Post-test odds = pre-test odds x likelihood ratio

where the likelihood ratio for a positive test result = sensitivity / (1 - specificity)

**Normal distribution**

The normal distribution is also known as the **Gaussian distribution** or '**bell-shaped distribution**'.

The Normal distribution **is a continuous** probability distribution.

It describes the spread of many biological and clinical measurements.

**Properties of the Normal distribution:**

- **Symmetrical** i.e. **Mean = Mode = Median**
- **68.3%** of values lie within **1 SD** of the mean.
- **95.4%** of values lie within **2 SD** of the mean.
- **99.7%** of values lie within **3 SD** of the mean.
- This is often reversed, so that within 1.96 SD of the mean lie 95% of the sample values
- The range of the mean - (1.96 \*SD) to the mean + (1.96 \* SD) is called the 95% confidence interval, i.e. If a repeat sample of 100 observations are taken from the same group 95 of them would be expected to lie in that range

**Standard deviation (SD):**

- The SD is a **measure** of **how much dispersion** exists from the **mean**.
- SD = square root (variance)

For normally distributed data **95.4% of values lie within 2** standard deviations of the mean, **leaving 4.6% outside** this range. Therefore **2.3%** of values will be higher and **2.3%** will be lower than 2 standard deviations from the mean. This figure is sometimes approximated to 2.5%

### Skewed distributions

**Normal** (Gaussian) distributions: mean = median = mode.

**Positively** skewed distribution: mean > median > mode.

**Negatively** skewed distribution mean < median < mode.

To remember the above note how they are **in alphabetical order**, think positive going forward with '>', whilst negative going backwards '<'

### Confidence interval and standard error of the mean (SEM)

The confidence interval is a common and sometimes misunderstood principle in medical statistics.

- A formal definition may be: a range of values for a variable of interest constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits.
- In simpler terms: **a range of values within which the true effect of intervention** is likely to lie.

The likelihood of the true effect lying within the confidence interval is determined by the confidence level.

For example a confidence interval at the 95% confidence level means that the confidence interval should contain the true effect of intervention 95% of the time.

#### How is the confidence interval calculated?

The standard error of the mean (SEM) is a measure of the spread expected for the mean of the observations - i.e. how 'accurate' the calculated sample mean is from the true population mean.

Key point:

$$\text{SEM} = \text{SD} / \text{square root (n)}$$

- (**SEM**) is Standard error of the mean.
- **SD** = standard deviation
- and **n** = sample size (number of patients)
- Therefore the SEM gets smaller as the sample size (n) increases.

**EX:** A small study looks at the weight of patients diagnosed with type 2 DM. Overall 64 patients were reviewed. The average weight was 81 kg, with a standard deviation of 12 kg.

The standard error of the mean =  $12 / \sqrt{64} = 12 / 8 = 1.5$

A 95% confidence interval:

- lower limit = mean - (1.96 \* SEM)
- upper limit = mean + (1.96 \* SEM)

The above formula is a slight simplification:

- If a small sample size is used (e.g.  $n < 100$ ) then it is important to use a 'Student's T critical value' look-up table to replace 1.96 with a different value.
- If a different confidence level is required, e.g. 90% then 1.96 is replaced by a different value. For 90% this would be 1.645.

### Funnel plot

A funnel plot is primarily used to demonstrate the **existence of publication bias in meta-analyses**.

**Funnel plots >>> show publication bias in meta-analyses**

Funnel plots are usually drawn with treatment effects on the horizontal axis and study size on the vertical axis.

Interpretation:

- A symmetrical, inverted funnel shape indicates that publication bias is unlikely.
- Conversely, an asymmetrical funnel indicates a relationship between treatment effect and study size. This indicates either publication bias or a systematic difference between smaller and larger studies ('small study effects').

### Study design: evidence and recommendations

#### Levels of evidence:

- 1) **Ia** - evidence from **meta-analysis** of **randomised controlled trials**
- 2) **Ib** - evidence from at least **one** randomised controlled **trial**
- 3) **Ila** - evidence from at least one well designed controlled trial which is not randomised

- 4) **IIb** - evidence from at least one well designed experimental trial
- 5) **III** - evidence from case, correlation and comparative studies
- 6) **IV** - evidence from a panel of **experts**

**Grading of recommendation:**

- **Grade A** - based on evidence from at least one randomised controlled trial (i.e. Ia or Ib)
- **Grade B** - based on evidence from non-randomised controlled trials (i.e. IIa, IIb or III)
- **Grade C** - based on evidence from a panel of experts (i.e. IV)

**Cell organelles**

The table below summarises the main functions of the major cell organelles:

Organelle/macromolecule	Main function
Endoplasmic reticulum	<p>Rough endoplasmic reticulum:</p> <ul style="list-style-type: none"><li>• translation and folding of new proteins</li><li>• manufacture of lysosomal enzymes</li><li>• site of N-linked glycosylation</li><li>• examples of cells with extensive RER include pancreatic cells, goblet cells, plasma cells</li></ul> <p><u>S</u>mooth endoplasmic reticulum:</p> <ul style="list-style-type: none"><li>• steroid, <b>lipid <u>s</u>ynthesis</b></li><li>• examples of cells with extensive SER include those of the adrenal cortex, hepatocytes, testes, ovaries</li></ul>



Organelle/macromolecule	Main function
Golgi apparatus	Modifies, sorts, and packages these molecules that are destined for cell secretion Site of O-linked glycosylation
<b>Mitochondrion</b>	Aerobic respiration. Contains mitochondrial genome as <b>double-stranded circular DNA</b>
Nucleus	DNA maintenance and RNA transcription
<b>Lysosome</b>	Breakdown of <b>large</b> molecules such as <b>proteins (peptides)</b> and polysaccharides
Nucleolus	Ribosome production
<b>Ribosome</b>	<b>Translation of RNA into proteins</b>
<u>Peroxisome</u>	Catabolism of very <u>long chain fatty acids</u> and <u>amino acids</u> Results in the formation of hydrogen peroxide ( <u>H<sub>2</sub>O<sub>2</sub></u> )
<b>Proteasome</b>	Along with the lysosome pathway involved in <b>degradation of protein</b> molecules that have been tagged with ubiquitin

## Cell cycle

Phase	Notes
<b>G<sub>0</sub></b>	<ul style="list-style-type: none"> <li>'resting' phase</li> <li>quiescent cells such as hepatocytes and more permanently resting cells such as neurons</li> </ul>
<b>G<sub>1</sub></b>	<ul style="list-style-type: none"> <li><b>Gap 1</b>, cells increase in size</li> <li>determines <b>length</b> of cell cycle</li> <li>under influence of <b>p53</b></li> </ul>
<b>S</b>	<ul style="list-style-type: none"> <li><b>Synthesis</b> of DNA, RNA and histone</li> <li>centrosome duplication</li> </ul>
<b>G<sub>2</sub></b>	<ul style="list-style-type: none"> <li><b>Gap 2</b>, cells continue to increase in size</li> </ul>
<b>M</b>	<ul style="list-style-type: none"> <li><b>Mitosis</b> - cell division</li> </ul>

## Cell division (see pic)

There are two types of cell division; mitosis and meiosis.

The table below demonstrates the key differences:

Mitosis	Meiosis
Occurs in <b>somatic</b> cells	Occurs in <b>gametes</b>
Results in <b>2 diploid</b> daughter cells	Results in <b>4 haploid</b> daughter cells
Daughter cells are genetically <b>identical</b> to parent cell	Daughter cells contain one homologue of each chromosome pair and are therefore genetically <b>different</b>

**Remember:**

- Somatic cells have 22 pairs of autosomes and 1 pair of sex chromosomes, i.e. 46XY or 46XX.
- Cells with a normal chromosome complement are known as **diploid** cells.
- Gametes (ova or spermatozoa) have a single copy of each chromosome and are known as **haploid** cells.

**Mitosis**

Mitosis occurs during the **M** phase of the cell cycle.

It describes the process in which somatic cells divide and replicate producing genetically identical diploid daughter cells.

This allows tissue to grow and renew itself.

During the S phase of the cell cycle the cell prepares itself for division by duplicating the chromosomes.

The table below shows the phases of mitosis itself:

<b>Prophase</b>	<b>Chromatin in the nucleus condenses</b>
<b>Prometaphase</b>	Nuclear membrane breaks down allowing the microtubules to attach to the chromosomes
<b>Metaphase</b>	Chromosomes aligned at <b>middle</b> of cell
<b>Anaphase</b>	The paired chromosomes separate at the kinetochores and move to opposite sides of the cell
<b>Telophase</b>	Chromatids arrive at opposite poles of cell
<b>Cytokinesis</b>	Actin-myosin complex in the centre of the cell contracts resulting in it being 'pinched' into two daughter cells

### Human genome

The human genome is stored on **23 chromosome pairs**.

The **haploid** human genome has a total of **3 billion DNA base pairs**, making up an estimated **20,000-25,000 protein-coding genes**.

<b>Human genome &gt;&gt; 25,000 protein-coding genes</b>
--

### Cervical cancer

The incidence of cervical cancer peaks around the 6th decade.

It may be divided into:

- **Squamous** cell cancer (**80%**)
- Adenocarcinoma (20%)

Features:

- May be detected during routine cervical cancer screening.
- Abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding.
- Vaginal discharge

Risk factors:

- **Human papilloma virus 16,18 & 33**
- HIV
- Smoking
- Early first intercourse, many sexual partners
- High parity
- Lower socioeconomic status
- Combined oral contraceptive pill

### Clusters of differentiation

The table below lists the major clusters of differentiation (CD) molecules:

Cluster of differentiation	Function
CD1	MHC molecule that presents lipid molecules.
CD2	Found on thymocytes, T cells, and some natural killer cells that acts as a ligand for CD58 and CD59 and is involved in signal transduction and cell adhesion.
CD3	The signalling component of the T cell receptor (TCR) complex.
CD4	Found on helper T cells. Co-receptor for MHC class II Used by HIV to enter T cells
CD5	Found in the majority of mantle cell lymphomas.
<b>CD8</b>	Found on cytotoxic T cells. Co-receptor for <b>MHC class I</b> Found on a subset of myeloid dendritic cells
CD14	Cell surface marker for macrophages.
CD15	Expressed on Reed-Sternberg cells (along with CD30).
CD28	Interacts with B7 on antigen presenting cell as costimulation signal.
CD95	Acts as the FAS receptor, involved in apoptosis.

**-CD4+ CD25+ Fox-P3 + T regulatory cells** are thought to be **the most important T regulatory cell population**. They are thought to play an important role in regulating immune responses after invading organisms have been tackled and preventing the development of autoimmunity.

-Regulatory T cells are **not** thought to produce IL-2.

-A small population of **CD8+** human regulatory T cells has been identified in addition to the larger population of CD4+ regulatory cells.

**-All T cells express the CD3 receptor**, and in humans only 5-10% of CD4+ cells are regulatory T cells.

### Lymphocytes

T and B lymphocytes express receptors on their surface that recognise antigen in a specific manner. Each individual lymphocyte expresses a single type of receptor with unique specificity (except dual specificity T cells - see below).

The receptor on the B lymphocyte is membrane bound immunoglobulin (IgM and IgD isotype) and recognises particulate antigen, whilst the T cell receptors TCR is a heterodimer that recognises peptide fragments presented by MHC molecules.

The antigen specificity of T and B cells is generated during development by recombination of gene segments encoding the variable domains (antigen recognition domains) of immune receptors. These gene recombinations are random and maturing lymphocytes that express autoreactive receptors which are then deleted or rendered anergic. These processes take place in the thymus (T lymphocytes) and in the bone marrow (B lymphocytes).

However, not all autoreactive lymphocytes are deleted during development. In the case of T lymphocytes, not all proteins are expressed in the thymus, and those that are present only in the periphery or at certain stages of development will encounter mature T cells that can respond to them. Thus, autoreactive T cells exist in the periphery and other mechanisms are responsible for the protection of the body against autoimmunity.

Affinity maturation refers to the process of progressive development of immunoglobulin with higher affinity to the antigen. This occurs in the germinal centres of lymphoid organs during the evolution of the humoral response and is accomplished by hypermutation of the variable region genes. T cells with dual specificities have been reported although their function is unknown.

### HLA associations

HLA antigens are encoded for by **genes** on **chromosome 6**.

HLA A, B and C are class I antigens whilst DP, DQ, DR are class II antigens.

Questions are often based around which diseases have strong HLA associations. The most important associations are listed below:

#### HLA-A3:

- Haemochromatosis

#### HLA-B5:

- Behcet's disease

#### HLA-B27:

- Ankylosing spondylitis
- Reiter's syndrome
- Acute anterior uveitis

#### HLA-DQ2/DQ8:

- Coeliac disease

#### HLA-DR2:

- Narcolepsy
- Goodpasture's

#### HLA-DR3:

- Dermatitis herpetiformis
- Sjogren's syndrome
- Primary biliary cirrhosis

#### HLA-DR4:

- Type 1 diabetes mellitus\*
- Rheumatoid arthritis

<b>HLA A3:</b> Haemochromatosis	<b>HLA-B5:</b> Behcet's disease	
	<b>HLA-B27:</b> <ol style="list-style-type: none"> <li>1. Ankylosing spondylitis</li> <li>2. Reiter's syndrome</li> <li>3. Acute anterior uveitis</li> </ol>	
	<b>HLA-B35:</b> Subacute thyroiditis	
	<b>HLA-DQ2/DQ8:</b> <ul style="list-style-type: none"> <li>• Coeliac disease</li> </ul>	<b>HLA-DR2:</b> <ol style="list-style-type: none"> <li>1. Narcolepsy.</li> <li>2. Goodpasture's.</li> </ol>
		<b>HLA-DR3:</b> <ol style="list-style-type: none"> <li>1) Primary biliary cirrhosis (also <b>DR8</b>).</li> <li>2) Sjogren's syndrome.</li> <li>3) Dermatitis herpetiformis.</li> </ol>
		<b>HLA-DR4:</b> <ul style="list-style-type: none"> <li>• DM T1</li> <li>• RA</li> </ul>

**NB:** DM T1 is associated with HLA-DR3 but is more strongly associated with HLA-DR4.

**NB:** Around **70%** of patients with **rheumatoid arthritis** are **HLA-DR4**. Patients with **Felty's syndrome** (a **triad** of rheumatoid arthritis, splenomegaly and neutropenia) are even more strongly associated with **90%** being **HLA-DR4**.



### Interleukin 1 (IL-1)

It is a key mediator of the immune response.

It is **secreted mainly by macrophages and monocytes** and acts as a **costimulator** of T cell and B cell proliferation.

Other effects include increasing the expression of adhesion molecules on the endothelium. By stimulating the release by the endothelium of **vasoactive** factors such as PAF, nitric oxide and prostacyclin it also causes **vasodilation** and increases vascular permeability.

It is therefore one of the **mediators of shock in sepsis**.

Along with IL-6 and TNF, it acts on the **hypothalamus** causing **pyrexia**.

### T-Helper cells

There are two major subsets of T-Helper cells:

#### Th1:

- Involved in the **cell mediated response** and **delayed (type IV) hypersensitivity**.
- Secrete **IFN-gamma, IL-2, and IL-3**.

#### Th2:

- Involved in mediating **humoral (antibody) immunity**.
- e.g. stimulating production of IgE in asthma
- Secrete **IL-4, IL-5, IL-6, IL-10, IL-13**

### Primary immunodeficiency

Primary immunodeficiency disorders may be classified according to which component of the immune system they affect.

**Neutrophil disorders:**

Disorder	Underlying defect	Notes
<b>Chronic granulomatous disease</b>	Lack of NADPH oxidase reduces ability of phagocytes to produce reactive oxygen species	Causes recurrent pneumonias and abscesses, particularly due to catalase-positive bacteria (e.g. Staphylococcus aureus) and fungi (e.g. Aspergillus)
<b>Chediak-Higashi syndrome</b>	Microtubule polymerization defect which leads to a decrease in phagocytosis	Affected children have 'partial albinism' and peripheral neuropathy. Recurrent bacterial infections are seen
<b>Leukocyte adhesion deficiency</b>	Defect of LFA-1 integrin (CD18) protein on neutrophils	Recurrent bacterial infections. Delay in umbilical cord sloughing may be seen

**B-cell disorders:**

Disorder	Underlying defect	Notes
<b>Common variable immunodeficiency (CVID)</b>	Many varying causes	<p>Hypogammaglobulinaemia is seen.</p> <p>May predispose to:</p> <ol style="list-style-type: none"> <li>1) Recurrent chest infection &gt;&gt;&gt; TTT: <b>IVIG</b>.</li> <li>2) Autoimmune disorders.</li> <li>3) Lymphoma.</li> <li>4) Predisposition to malignancy.</li> </ol>

Disorder	Underlying defect	Notes
<b>Bruton's congenital agammaglobulinaemia</b>	Defect in Bruton's tyrosine kinase (BTK) gene that leads to a severe block in B cell development	X-linked recessive. Recurrent bacterial infections are seen
<b>Selective immunoglobulin A deficiency</b>	Maturation defect in B cells	Most common primary antibody deficiency. Recurrent sinus and respiratory infections

**T-cell disorders:**

Disorder	Underlying defect	Notes
<b>DiGeorge syndrome</b>	22q11.2 <b>deletion</b> , failure to develop 3rd and 4th pharyngeal pouches	Common features include congenital heart disease, learning difficulties, <b>hypocalcaemia</b> (dt: parathyroid gland hypoplasia), thymus hypoplasia, recurrent <b>viral/fungal</b> diseases.

**Combined B- and T-cell disorders:**

Disorder	Underlying defect	Notes
<b>Severe combined immunodeficiency (SCID)</b>	Many varying causes. Most common (X-linked) due to defect in the common gamma chain, a protein used in the receptors for IL-2 and other interleukins. Other causes include adenosine deaminase deficiency	Recurrent infections due to viruses, bacteria and fungi. Stem cell transplantation may be successful

Disorder	Underlying defect	Notes
<b>Ataxia telangiectasia</b>	Defect in DNA repair enzymes	Autosomal recessive. Features include cerebellar ataxia, telangiectasia, recurrent chest infections and 10% risk of developing malignancy, lymphoma or leukaemia
<b>Wiskott-Aldrich syndrome (WAS)</b>	Defect in <b>WASP gene</b>	<p><b>X-linked recessive.</b> Features include <b>(4)</b>:</p> <ul style="list-style-type: none"> <li>• Recurrent bacterial infections (Chest)+</li> <li>• Eczema+</li> <li>• Low PLT+</li> <li>• Low IgM levels.</li> </ul> <p>At ↑ risk of lymphoreticular malignancy.</p>

1 ry Immunodeficiency dt **Combined** B- and T-cell disorders are >>>

**SCID+ WAS+ Ataxic** (SCID, Wiskott-Aldrich syndrome, ataxic telangiectasia).

**EX:** Male pt. 20 years old has recurrent oesophageal candidiasis, also has asthma on steroids, eczema, No B cells, Low Igs, low PLT, normal CD count (so NOT HIV)  
>>> **Primary** immunodeficiency (**Wiskott-Aldrich Syndrome**).

### Metabolic acidosis

Metabolic acidosis is commonly classified according to the anion gap.

This can be calculated by: **(Na<sup>+</sup> + K<sup>+</sup>) - (Cl<sup>-</sup> + HCO<sub>3</sub><sup>-</sup>)**.

If a question supplies the **chloride** level then this is often a clue that the anion gap should be calculated.

The normal range = **10-18 mmol/L**.

In **normal** anion gap metabolic acidosis, **chloride** is **retained** to balance the charge of the  $\text{HCO}_3$  ions, which are lost. So it is also called **hyperchloraemic** metabolic acidosis. (Chloride N= 95-110 mmol/L).

Normal anion gap (=hyperchloraemic metabolic acidosis)	Raised anion gap
<ol style="list-style-type: none"> <li>1) <b><math>\text{HCO}_3</math> loss</b> from <b>GIT</b>: diarrhoea, ileostomy, ureterosigmoidostomy, fistula.</li> <li>2) <b><math>\text{HCO}_3</math> loss</b> from <b>kidneys</b>: <ul style="list-style-type: none"> <li>○ <b>RTA (type 2)</b> (proximal).</li> <li>○ <b>Drugs</b>: e.g. <b>acetazolamide</b>.</li> <li>○ <b>Tubular damage</b>.</li> <li>○ <b>Hyperparathyroidism</b>.</li> </ul> </li> <li>3) <b>Decreased <math>\text{H}^+</math> ion excretion</b> from the <b>kidneys</b>: <ul style="list-style-type: none"> <li>○ <b>RTA (type 1)</b> (distal).</li> <li>○ <b>RTA (type 4)</b>.</li> </ul> </li> <li>4) <b>Ammonium chloride</b> injection.</li> <li>5) <b>Addison's</b> disease.</li> </ol>	<ol style="list-style-type: none"> <li>1) <b>DKA</b>.</li> <li>2) <b>Renal failure</b>.</li> <li>3) <b>Salicylates</b> poisoning.</li> <li>4) <b>Alcohol, methanol, Ethylene glycol</b></li> <li>5) <b>Lactic acidosis</b>: type A&amp;B.</li> </ol>

Metabolic acidosis secondary to high lactate levels is subdivided into two types:

- Lactic acidosis **type A**: shock, hypoxia, burns.
- Lactic acidosis **type B**: drugs: Metformin, TCA.

### Metabolic alkalosis

Metabolic alkalosis may be caused by a loss of hydrogen ions or a gain of bicarbonate.

It is due mainly to problems of the kidney or gastrointestinal tract.

Alkalosis is more unusual clinically than acidosis and has fewer causes.

Maintaining an alkalosis is also more difficult as the body produces significant amounts of acid each day during normal metabolism.

Causes:

- 1) **Hypokalaemia** (see next)
- 2) **Vomiting / aspiration** (e.g. anorexia nervosa, peptic ulcer leading to pyloric stenosis, gastric outlet obstruction, **nasogastric suction**)
- 3) **Diuretics**
- 4) **Burns**
- 5) **Liquorice, carbenoxolone**
- 6) **Conn's (Primary hyperaldosteronism)**
- 7) **Cushing's** syndrome
- 8) **Bartter's** syndrome
- 9) **Congenital adrenal hyperplasia**

Mechanism of metabolic alkalosis:

- Activation of renin-angiotensin II-aldosterone (RAA) system is a key factor.
- Aldosterone causes reabsorption of  $\text{Na}^+$  in exchange for  $\text{H}^+$  in the distal convoluted tubule.
- ECF depletion (vomiting, diuretics)  $\rightarrow$   $\text{Na}^+$  and  $\text{Cl}^-$  loss  $\rightarrow$  activation of RAA system  $\rightarrow$  raised aldosterone levels.
- In hypokalaemia,  $\text{K}^+$  shift from cells  $\rightarrow$  ECF, alkalosis is caused by shift of  $\text{H}^+$  into cells to maintain neutrality.

### Respiratory alkalosis

Causes of respiratory alkalosis:

- Central causes - stroke, meningitis, CNS tumour
- Drugs - salicylates
- Anxiety
- Pregnancy.

### Hypokalaemia and acid-base balance

Potassium and hydrogen can be thought of as competitors.

**Hyperkalaemia** tends to be associated with **acidosis** because as potassium levels rise fewer hydrogen ions can enter the cells.

Hypokalaemia with acidosis:	Hypokalaemia with alkalosis:
1) <b>Partially treated DKA</b> 2) <b>Renal tubular acidosis</b> 3) <b>Diarrhoea</b> 4) <b>Acetazolamide</b>	1) <b>Vomiting</b> 2) <b>Diuretics</b> 3) <b>Cushing's</b> syndrome 4) <b>Conn's</b> syndrome

**Magnesium deficiency** may also cause hypokalaemia. In such cases, normalizing the potassium level may be difficult until the magnesium deficiency has been corrected.

Approximately a **drop of 1 mmol in serum potassium** is equivalent to a **total body loss of 200 mmol of potassium**.

### Hyperkalaemia

Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and insulin levels.

**Metabolic acidosis** is associated with **hyperkalaemia** as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule.

**ECG** changes seen in hyperkalaemia include **tall-tented T waves**, small P waves, **prolonged PR interval**, **widened QRS** leading to a sinusoidal pattern and asystole.

Causes of hyperkalaemia:

- 1) **Firstly exclude pseudo-hyperkalaemia** >> Re-check a fresh sample.
- 2) **Acute renal failure**
- 3) **Metabolic acidosis**
- 4) **Addison's**
- 5) **Rhabdomyolysis**
- 6) **Massive blood transfusion**
- 7) **Drugs: Aldactone, ACEIs, ARBs, Cyclosporine, Heparin (UFH & LMWH), Beta blockers.**

Both **UFH** and **LMWH** can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

**Beta-blockers** interfere with potassium transport into cells and can potentially cause hyperkalaemia in renal failure patients - remember beta-agonists, e.g. Salbutamol, are sometimes used as emergency treatment.

**Pseudohyperkalaemia** is known to be associated with **essential thrombocytosis**, and patients with essential thrombocytosis are at increased risk of **gout**, and any prescription of **Lasix** will only make the problem worse.

Foods that are high in potassium:

- Salt substitutes (i.e. contain potassium rather than sodium).
- **Bananas, oranges, kiwi fruit, avocado, spinach, tomatoes.**

The most appropriate initial therapy of hyperkalaemia is **protection of the heart** by **IV calcium gluconate** which acts within **minutes** and works by **raising the depolarization threshold for myocytes**.

Other medical ttt to lower K level (cell shift) is: **15 units actrapid insulin in 50 ml dextrose 50%, salbutamol nebulizer, NaHCO3 IV** (debatable, can worsen volume overload esp. in renal imp and pulmonary oedema).

**Calcium resonium** is an ion exchange resin which, when taken orally, prevents potassium from being absorbed in the diet. It acts to deplete the body of potassium (by preventing absorption) and **takes at least 24-48 hours to have an effect**. It is not suitable as an emergency treatment.



Guidelines for **surgery** in patients with **CRF** suggest that surgery should be postponed **until serum K below 5.5 mmol/l** and also K should be monitored **immediately** after surgery and then again **4-6 hours later**.

### Hyponatraemia

Hyponatraemia may be caused by water excess or sodium depletion.

Causes of **pseudohyponatraemia** include (High blood lipid or protein):

- **Hyperlipidaemia** (increase in serum volume) as in nephrotic syndrome or
- **Hyperproteinaemia** as in myeloma.
- **Taking blood from a drip arm.**

Urinary sodium and osmolality levels aid making a diagnosis.

It is important to diagnose pseudohyponatraemia, **because as the plasma osmolality is normal no treatment is required.**

### Urinary sodium > 20 mmol/l:

Sodium depletion, renal loss (patient often hypovolemic):

- 1) Addison's
- 2) Diuretics
- 3) Diuretic stage of renal failure

Patient often euvolaemic:

- 1) SIADH (urine osmolality > 500 mmol/kg)
- 2) Hypothyroidism

### Urinary sodium < 20 mmol/l:

Sodium depletion, extra-renal loss:

- Diarrhoea, vomiting, sweating
- Burns, adenoma of rectum

Water excess (patient often hypervolaemic and oedematous):

- Secondary hyperaldosteronism: heart failure, cirrhosis.
- Reduced GFR: renal failure.
- IV dextrose, psychogenic polydipsia.

In Hyponatraemia >>>> Check Urinary NA			
Urinary sodium > 20 mmol/l		Urinary sodium < 20 mmol/l	
Hypovolemic (Na depletion, <b>Renal</b> loss)	Euvolaemic	Hypervolaemic	Hypovolemic (Na depletion, <b>Extra-renal</b> loss)  (as pre-renal azotaemia)
-Addison's. -Diuretics. -Diuretic stage of ARF.	<b>-SIADH:</b> (High urine osmolality > 500 mmol/kg) - Hypothyroidism	-Secondary hyperaldosteronism: CHF, L cirrhosis, Nephrotic S. -Reduced GFR: renal failure. -Psychogenic polydipsia. -IV dextrose.	-Diarrhoea. -Vomiting. -Sweating. -Burns. -Adenoma of rectum.

**Beer potomania** is a recognized cause of **hyponatraemia** in **alcohol misusers**, there is **osmolar gap** due to presence of osmotically active ethanol in the blood, and the electrolyte imbalance **normally corrects** itself with **cessation** of alcohol.

Patients with chronic liver disease and ascites often develop hyponatraemia, the management of which can be difficult.

Diuretic therapy for the management of ascites often contributes to the hyponatraemia.

The British Society of Gastroenterology guidelines suggest that where the **serum sodium is  $\leq 120$  mmol/L >>> diuretic therapy should be stopped and give the patients **volume expansion** with **colloid** or **normal saline**.**

No specific intervention other than careful **monitoring** is advised where the serum sodium is **126-135** mmol/L.

In the range **121-125** mmol/L where the serum creatinine is normal, **diuretic** therapy may be continued but may need to be **reduced** with a view to stopping if necessary.

If the sodium is in this range but the serum creatinine is rising diuretics should be stopped and patients should receive volume expansion.

These guidelines also advise that **fluid restriction** should only be used in patients who are clinically **euvolaemic**, **not on diuretics** and have severe hyponatraemia with a normal serum creatinine.

**EX:** Pt. with CLD and ascites on diuretics with serum Na 115 mmol/L >>> **Stop diuretics and give normal saline.**

#### **SIADH (The syndrome of inappropriate ADH secretion): causes**

SIADH is characterised by **hyponatraemia** secondary to the **dilutional effects** of **excessive water retention**.

#### **Criteria:**

- 1) **Normal Renal, Normal Adrenal and Normal Thyroid.**
- 2) Hyponatraemia < 135 mEq/l
- 3) Hypotonic plasma **P**osmo < 270 mOsm/Kg
- 4) Inappropriate ↑ urine osmolality
- 5) ↑ Urine Na > 20 mEq/L

#### **Causes of SIADH:**

Category	Examples
Malignancy	<ul style="list-style-type: none"><li>• <b>Small cell lung cancer (SCLC)</b></li><li>• also: pancreas, prostate</li></ul>
Neurological	<ul style="list-style-type: none"><li>• Stroke</li><li>• Subarachnoid haemorrhage</li><li>• Subdural haemorrhage</li><li>• Meningitis/encephalitis/abscess</li></ul>

Category	Examples
Infections	<ul style="list-style-type: none"> <li>• Tuberculosis</li> <li>• Pneumonia</li> </ul>
Drugs	<ul style="list-style-type: none"> <li>• <b>Sulfonylureas</b></li> <li>• <b>SSRIs</b></li> <li>• <b>TCA</b></li> <li>• <b>Carbamazepine</b></li> <li>• <b>Thiazide</b></li> <li>• Vincristine</li> <li>• Cyclophosphamide</li> </ul>
Other causes	<ul style="list-style-type: none"> <li>• Positive end-expiratory pressure (PEEP)</li> <li>• <b>Porphyrias</b></li> </ul>

**Management:**

- 1) Correction must be done **slowly** to **avoid** precipitating **central pontine myelinolysis (CPM)**.
- 2) **Fluid restriction.**
- 3) **Demeclocycline oral**: reduces the responsiveness of the collecting tubule cells to ADH >> **it will induce nephrogenic D.I.** it is used for SIADH when fluid restriction alone is inadequate.
- 4) **ADH (vasopressin) receptor antagonists** have been developed.

NB: Lithium induces nephrogenic DI but is not an appropriate ttt for SIADH.

**N.B: Other points to diagnose SIADH:**

- Maintained hypervolemia.
- Suppression of RAS (renin angiotensin system)
- No equal concentration of ANP (atrial natriuretic peptide)
- Normal serum creatinine.
- Normal acid base and K balance.
- ↓ BUN
- ↓ Uric acid
- ↓ Albumin

**Antidiuretic hormone (ADH)**

ADH is a **nona-peptide** manufactured in the **supra-optic (SO)** and **paraventricular (PV) nuclei** of the **hypothalamus** and released (secreted) from the **posterior** pituitary.

It acts on the **collecting ducts** improving water permeability and hence water retention.

It promotes water reabsorption in the collecting ducts of the kidneys by the **insertion of aquaporin-2 channels**.

Carbamazepine as well as other agents such as thiazides and SSRIs may potentiate its release.

Ethanol usually inhibits release.

Antidiuretic hormone (ADH) >>> site of action >>> collecting ducts

**Hypernatraemia**

Causes of hypernatraemia:

- 1) **Severe Dehydration.**
- 2) **Diabetes insipidus.**
- 3) Osmotic diuresis e.g. **Hyperosmolar** non-ketotic diabetic coma (HHS).
- 4) **Excess IV saline**

Hypernatraemia should be corrected with great caution.

Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema, resulting in seizures, coma and death.

Although there are no clinical guidelines by NICE or Royal College of Physicians at present, it is generally accepted that **a rate of no greater than 0.5 mmol/hour correction is appropriate**.

**EX:** A 74-year-old gentleman with **dementia** is admitted from the nursing staff, with worsening confusion and inability to eat and drink.

He is clinically dehydrated and his **serum Na** is measured at **168** mmol/litre.

Assuming the normal serum sodium value is 140 mmol/litre, and **his total body water is 40 litres**, calculate the free water deficit.

**The free water deficit in litre calculation** is as follows:

(Patient sodium-140)/ 140) x total body water (TBW) = free water deficit in litres.  
(168-140/140) X 40 = **8 litres**.

### **Osmolality and Osmolarity**

The **osmolar gap** is the difference between the **calculated osmolarity** and the **measured osmolality**.

Osmolar gap= Calculated Osmolarity (Osmol/L) – Lab Osmolality (Osmol/Kg)

The normal value is **10-15** but may be increased in the presence of unmeasured 'abnormal' osmotically active ions in the plasma.

**Osmolarity** is the measure of solute concentration, defined as the number of osmoles (Osm) of solute per litre (l) of solution (**Osmol/l**).

**Calculated osmolarity = 2 (Na + K) + Glucose + Urea (all in mmol/L).**

2 (132 + 4) + 5 + 7 = 306 mOsm/L

**Normal serum osmolarity is 285-295 mOsm/L.**

Osmolarity can be affected by temperature and pressure and for a given solution, this calculated variable is less than the osmolality.

**Osmolality** is also a measure of solute concentration but is defined as the number of osmoles (Osm) of solute per kilogram (**Osm/Kg**).

The value is independent of temperature and pressure. It is measured in the **laboratory** using an **osmometer**. Osmometers use the colligative properties of a solution such as depression of freezing point or vapour pressure.

Osmolar gap = Osmolality – osmolarity = 324 – 284 = 40

An elevated osmolar gap provides indirect evidence for the presence of an **abnormal solute** that may be present in significant amounts.

To have much effect on the osmolar gap, this substance needs to have a low molecular weight and be uncharged so it can be present in a form and in a concentration (measured in mmol/l) sufficient to elevate the osmolar gap.

**Ethanol**, **ethylene glycol** (anti-freeze), **acetone** and **methanol** are solutes that will cause elevation of the osmolar gap in this way.

### Hypomagnesaemia

Cause of low magnesium:

- 1) **Diuretics**
- 2) Diarrhoea
- 3) TPN (Total parenteral nutrition)
- 4) Alcohol
- 5) Hypokalaemia, Hypocalcaemia

Features:

- 1) Paraesthesia
- 2) Tetany
- 3) Seizures
- 4) Arrhythmias
- 5) Decreased PTH secretion → hypocalcaemia
- 6) ECG features similar to those of hypokalaemia
- 7) Exacerbates digoxin toxicity

## Hypophosphatemia

The three major mechanisms of hypophosphatemia are:

- 1) **Redistribution** of extracellular phosphate into cells
- 2) Decreased **intestinal absorption** and
- 3) Depletion due to increased **urinary loss**

Causes:

- 1) **Alcohol excess**
- 2) **Acute liver failure**
- 3) **Primary hyperparathyroidism**
- 4) **Osteomalacia**
- 5) **DKA**
- 6) **Refeeding syndrome**

Consequences:

- Red blood cell haemolysis
- White blood cell and platelet dysfunction
- Muscle weakness and rhabdomyolysis
- Central nervous system dysfunction

**EX:** A 19-year-old female with a history of **anorexia nervosa** is admitted to hospital. Her BMI has dropped to 16. She has agreed to be fed by **nasogastric tube (NGT)**. Which one of the electrolyte disturbances is most likely to occur? >>> This patient is at risk of **refeeding syndrome**, which can lead to **profound hypophosphatemia**.

**Refeeding syndrome** occurs when **malnourished** individuals are given nutritional support (or simply recommence food intake).

Individuals need only to have been starved for as little as 5 days to be at risk.

Patients may present with symptoms ranging from weakness to alterations in mental state, neurological abnormalities (dysarthria, diplopia) and rhabdomyolysis.

The **triad of electrolyte** abnormalities of (**K**, **Mg**, and **Po4**), **hypokalaemia**, **hypomagnesaemia** and **hypophosphatemia** are characteristic.

Management:



**1) Correcting electrolyte abnormalities** aggressively IV or orally.

**2)** Carefully controlling calorific intake: **Calorie intake may need to be reduced** to less than 50% of the recommended amount.

**NB:** Supplementary **NG** feeding is usually **NOT** indicated.

**NB:** **TPN** does **NOT** offer any significant advantage over oral feeding and is associated with significant complications; where there is an intact gut feeding should be via this route.

When a patient **hyperventilates**, there is a rise in intracellular pH (fall in partial pressure of carbon dioxide, which can readily diffuse across cell membranes). The rise in pH then stimulates phosphofructokinase activity, which in turn activates glycolysis.

So, **painful venepuncture >> Hyperventilation >> low serum Phosphate**

**Oncogenic hypo-phosphataemic osteomalacia and x linked hypophosphataemic rickets** belong to the third mechanism of urinary excretion.

### Complement deficiencies

Complement is a series of proteins that circulate in plasma and are involved in the inflammatory and immune reaction of the body.

Complement proteins are involved in chemotaxis, cell lysis and opsonisation.

#### **C1 inhibitor (C1-INH) protein deficiency:**

- Causes **hereditary angioedema**.
- C1-INH is a multifunctional serine protease inhibitor.
- Probable mechanism is uncontrolled release of bradykinin resulting in oedema of tissues.

#### **C1q, C1rs, C2, C4 deficiency (classical pathway components):**

- Predisposes to **immune complex disease**.
- e.g. **SLE, Henoch-Schonlein Purpura**.

#### **C3 deficiency:**

- Causes **recurrent bacterial** infections.

**C5 deficiency:**

- Predisposes to **Leiner disease**.
- Recurrent diarrhoea, wasting and **seborrhoeic dermatitis**.

**C5-9 deficiency:**

- Encodes the **membrane attack complex (MAC)**.
- Particularly prone to **Neisseria meningitidis** infection.

**EX:** Pt with deficiencies of which one of the complement proteins are most predisposed to **disseminated meningococcal infection**? >> **C5**.

Whilst C3 deficiency is associated with recurrent bacterial infections, **C5** deficiency is more characteristically associated with **disseminated meningococcal infection** and **other Gram negative diplococcal** infections like **Neisseria gonorrhoeae**.

**Hereditary angioedema (HAE)**

Hereditary angioedema is an **autosomal dominant** condition associated with **low plasma** levels of the **C1 inhibitor (C1-INH) protein**.

C1-INH is a multifunctional serine protease inhibitor - the probable mechanism behind attacks is uncontrolled release of **bradykinin** resulting in oedema of tissues. (**NOT** Histamine).

Investigation:

- **C1-INH** level is **low during** an attack.
- **Low C2** and **C4** levels are seen, **even between attacks**.
- **Serum C4** is the most reliable and widely used **screening** tool.

Hereditary angioedema >>> **C1-INH** level is **low during** an attack.

**C4** is the **best screening** test **in-between attacks**.

Symptoms:

- Attacks may be preceded by painful macular rash.
- Painless, non-pruritic swelling of subcutaneous/submucosal tissues.

- May affect upper airways, skin or abdominal organs (can occasionally present as abdominal pain due to visceral oedema).
- Urticaria is not usually a feature.

Management:

- **Acute**: IV C1-inhibitor concentrate, fresh frozen plasma (FFP) if this is not available.
- **Prophylaxis**: anabolic steroid Danazol may help.

### Immunoglobulins

The table below summarises the characteristics of the 5 types of immunoglobulin found in the body:

<b>IgG</b>	<b>75%</b>	Monomer	Enhance <b>phagocytosis</b> of bacteria and viruses, <b>pass to fetal circulation</b> .
<b>IgA</b>	<b>15%</b>	Monomer/ dimer	Found in <b>secretions</b> , provide localized protection on mucous membranes
<b>IgM</b>	<b>10%</b>	<b>Pentamer</b>	<b>First</b> to be secreted, anti-A, B <b>blood</b> antibodies. It is responsible for <b>haemolytic blood transfusion reactions</b> .
<b>IgD</b>	<b>1%</b>	Monomer	Involved in <b>activation of B cells</b>
<b>IgE</b>	<b>0.1%</b>	Monomer	Involved in <b>allergic</b> reactions anaphylaxis, asthma and atopy.  Involved in <b>type I hypersensitivity</b> reaction.

Whilst the **majority** of **IgA** is found in **secretions** there is a significant quantity present in **blood**. IgE makes up **less than 0.1% of immunoglobulins**. It is the immunoglobulins which is present **in the lowest concentration in blood**.

**Total serum IgE** is frequently increased in those with **atopy** but serum IgE does **not** rise **acutely** during an **asthmatic** attack.

**EX**: Patient with **repeated** chest and sinuses infections with **encapsulated** bacteria like *Streptococcus pneumoniae* and *Haemophilus influenzae* which should raise the suspicion of **immunoglobulin deficiency (IgA)**.

**IgA deficiency**, in **Caucasians**, is said to occur in **1 in 600-700** individuals. There is often a **deficient response to polysaccharide-based vaccinations** such as **HBV** and **tetanus**.

In patients with IgA deficiency, 10-44% of patients **may have anti-IgA antibodies**; this risks a **severe reaction to** IgA-containing products such as blood, plasma or immunoglobulin.

**EX:** Female patient 35 years old, with flu like illness, 10-year history of tendency to have a blocked, stuffy nose and frequent recurrent coughs and colds >>>? **IgA deficiency**.

HIV would be suggested by infections associated with impaired cellular immunity.

#### **Immune system cells: innate immune response**

The following cells are mostly involved in the innate immune response:

<b>Cell type</b>	<b>Functions and properties</b>
<b>Neutrophil</b>	Primary phagocytic cell in acute inflammation Granules contain myeloperoxidase and lysozyme Most common type of white blood cell Multi-lobed nucleus
<b><u>Basophil</u></b>	Releases histamine during allergic response Granules contain <b>histamine</b> and <b>heparin</b> Expresses IgE receptors on the cell surface Bi-lobed nucleus
<b><u>Mast cell</u></b>	Present in tissues and are similar in function to basophils but derived from different cell lines Granules contain <b>histamine</b> and <b>heparin</b> Expresses IgE receptors on the cell surface
<b>Eosinophil</b>	Defends against protozoan and helminthic infections Bi-lobed nucleus

Cell type	Functions and properties
<b>Monocyte</b>	Differentiates into macrophages Kidney shaped nucleus
<b>Macrophage</b>	Involved in <b>phagocytosis</b> of cellular debris and pathogens. Acts as an antigen presenting cell ( <b>APC</b> ). Major source of <b>IL-1</b> .  <b>Foam cells</b> are fat-laden macrophages.
<b>Natural killer cell (NK)</b>	Induce <b>apoptosis</b> in virally infected and tumour cells
<b>Dendritic cell</b>	Acts as an antigen presenting cell (APC)

#### Autosomal dominant conditions

Kindly note that: Autosomal **recessive** conditions are often thought to be '**metabolic**' as opposed to autosomal **dominant** conditions being '**structural**', notable exceptions:

- Some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive, whilst others such as hyperlipidaemia type II and hypokalaemic periodic paralysis are autosomal dominant.
- Some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive.

- **Autosomal dominant** conditions are '**structural**' - exceptions: hyperlipidaemia type II, hypokalaemic periodic paralysis.
- **Autosomal recessive** conditions are '**metabolic**' - exceptions: inherited Friedreich's ataxias, ataxia telangiectasia.

In autosomal dominant diseases:

- **Both homozygotes and heterozygotes manifest disease** (there is **no carrier state**)

- **Both males and females** affected
- Only affected individuals can pass on disease
- Disease is **passed on to 50% of children**
- Normally appears in every generation (although see below)
- **Risk remains same for each successive pregnancy**

Complicating factors:

- **Non-penetrance:** (i.e. **affected individuals do not always have affected parents**) lack of clinical signs and symptoms (normal phenotype) despite abnormal gene. E.g. 40% otosclerosis
- Spontaneous mutation: new mutation in one of gametes e.g. 80% of individuals with achondroplasia have unaffected parents

**The following conditions are autosomal dominant:**

- 1) **Achondroplasia**
- 2) **Acute intermittent porphyria**
- 3) **Adult polycystic disease**
- 4) **Antithrombin III deficiency**
- 5) Ehlers-Danlos syndrome
- 6) Familial adenomatous polyposis (**FAP**)
- 7) **Hereditary haemorrhagic telangiectasia**
- 8) **Hereditary spherocytosis**
- 9) Hereditary non-polyposis colorectal carcinoma
- 10) **Huntington's disease**
- 11) **Hyperlipidaemia type II**
- 12) **Hypokalaemic periodic paralysis**
- 13) **Malignant hyperthermia**
- 14) **Marfan's syndromes**
- 15) **Myotonic dystrophy**
- 16) Neurofibromatosis
- 17) **Noonan syndrome**
- 18) Osteogenesis imperfecta

- 19) Peutz-Jeghers syndrome
- 20) **Retinoblastoma**
- 21) Romano-Ward syndrome
- 22) **Tuberose sclerosis**
- 23) Von Hippel-Lindau syndrome
- 24) **Von Willebrand's disease.**

Type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

#### Autosomal recessive conditions

In autosomal recessive inheritance:

- **Only homozygotes** are affected
- Males and females are **equally likely** to be affected
- Not manifest in every generation - may '**skip a generation**'

**If one affected parent (i.e. homozygote for gene) and one unaffected (i.e. not a carrier or affected):**

- **ALL** the children will be **carriers**.

**If two heterozygote parents:**

- **25%** chance of having an affected (homozygote) child
- **50%** chance of having a carrier (heterozygote) child
- **25%** chance of having an unaffected (i.e. genotypical) child

**Autosomal recessive disorders** are **often metabolic** in nature and are generally **more life-threatening compared to autosomal dominant** conditions.

**The following conditions are autosomal recessive:**

- 1) **Albinism**
- 2) Ataxia telangiectasia

- 3) **Congenital adrenal hyperplasia**
- 4) **Cystic fibrosis**
- 5) Cystinuria
- 6) Familial Mediterranean Fever
- 7) Fanconi anaemia
- 8) **Friedreich's ataxia**
- 9) **Gilbert's** syndrome: this is still a matter of debate and many textbooks will list Gilbert's as autosomal dominant.
- 10) Glycogen storage disease
- 11) Haemochromatosis
- 12) Homocystinuria
- 13) Lipid storage disease: Tay-Sach's, Gaucher, Niemann-Pick
- 14) Mucopolysaccharidoses: Hurler's
- 15) PKU
- 16) **Sickle cell anaemia**
- 17) **Thalassaemias**
- 18) **Wilson's** disease

As cystic fibrosis is an autosomal recessive condition there is a **50%** chance that their next child will be a **carrier** of cystic fibrosis (i.e. be heterozygous for the genetic defect) and a **25%** chance that the child will **actually have** the disease (be homozygous) and **25%** chance to be **free**.

### **X-linked recessive**

In X-linked recessive inheritance **only males are affected**.

An **exception** to this seen in examinations are patients (females) with **Turner's syndrome**, who are affected due to **only having one X chromosome**.

X-linked recessive disorders are **transmitted by heterozygote females (carriers)** and **NO male-to-male transmission**.

Males will pass on the **'bad' X chromosome** to their **daughters** so that they become **carriers**, they are **not** usually affected as they will have a 'good' X from the normal mothers, **Males** pass on their **Y** chromosomes to any sons, therefore they will **not** be affected.



So male with G6PD + Normal female >>>> All children will not be affected, but the daughters will be carrier to be affect the incoming their boys.

**Affected males** can have **unaffected sons** and **carrier daughters**.

As **his sons** will get the X chromosome from his wife and so will not be carriers but all **his daughters** will be carriers.

X-linked recessive conditions >>> there is **no male-to-male transmission**. **Affected males** can only have **unaffected sons** and **carrier daughters**.

And one of **his relatives** is most likely to have the condition is >> **his Mother's father** جد أمه

هذا الرجل لن يصيب اولاده البنين او البنات .. ولكن بناته ستكون حاملة للمرض لتنتقله الى احفاده البنين

His daughters' sons will consequently have a 50% chance of inheriting the disease as **all his daughters are carriers** and there is a **1 in 2 chance (50:50)** of **passing the gene on to their sons**.

Haemophilia is an X-linked recessive disorder and would hence be expected **only** to occur in **males**. With exception that only appears in **female** patient if with **Turner's syndrome** **only have one X chromosome** however, they may develop X-linked recessive conditions.

A 14-year-old **girl** presents with a swollen left knee. She suffers from **haemophilia** and has been treated for a right-sided haemarthrosis previously. What other condition is she most likely to have >> **Turner's syndrome**.

Each **male** child of a heterozygous female carrier has a **50% chance of being affected** whilst each **female** child of a heterozygous female carrier has a **50% chance of being a carrier**.

The possibility of an affected father having children with a heterozygous female carrier is generally speaking extremely rare. However, in certain Afro-Caribbean communities G6PD deficiency is relatively common and homozygous females with clinical manifestations of the enzyme defect are seen.

**The following conditions are inherited in an X-linked recessive fashion:**

- 1) **Androgen insensitivity syndrome**
- 2) **Becker** muscular dystrophy
- 3) **Duchenne** muscular dystrophy

- 4) **Fabry's disease**
- 5) **G6PD deficiency**
- 6) **Haemophilia A,B**
- 7) Hunter's disease
- 8) Lesch-Nyhan syndrome
- 9) Nephrogenic diabetes insipidus
- 10) **Colour blindness**
- 11) **Ocular albinism**
- 12) **Retinitis pigmentosa**
- 13) **Wiskott-Aldrich syndrome (WAS)**
- 14) Chronic granulomatous disease: it has varying patterns of inheritance, with the majority being in an X-linked recessive fashion (in > 70%).

### X-linked dominant

The following conditions are inherited in an X-linked dominant fashion:

- 1) **Alport's syndrome** (see nephrology) :( in around 85% of cases - 10-15% of cases are inherited in an autosomal recessive fashion with rare autosomal dominant variants existing).
- 2) **Vitamin D resistant rickets.**
- 3) **Rett syndrome.**

**NB:** Pseudohypoparathyroidism was previously classified as an X-linked dominant condition but has now been shown to be inherited in an autosomal dominant fashion in the majority of cases.

### Achondroplasia

Achondroplasia an **autosomal dominant** condition and one of the commonest forms of short-limbed dwarfism.

It is caused by an activated point-mutation of the fibroblast growth factor receptor 3 (at 4p16.3).

The incidence increases **with paternal age**.

**Epiphyseal growth cartilage fails**, but there is **normal bone formation** and **repair**. There is therefore **no increased risk of fracture**. The homozygous form is usually fatal.

Affected persons have short stature due to **shortening of the limbs**, but **spinal length is maintained**. In addition they have characteristic facies with frontal bossing

and mid-face hypoplasia, **exaggerated lumbar lordosis**, limited elbow extension and trident-like hands. The fingertips may only come down to the iliac crest, and the shortness of the limbs is often most marked proximally. The limbs appear broad with deep creases.

It **may be diagnosed radiographically at birth**, or becomes obvious within the first year with disparity between a large skull, normal trunk length and short limbs. x Rays show metaphyseal irregularity, flaring in the long bones, and late-appearing irregular epiphyses. The pelvis is narrow in anteroposterior diameter with deep sacroiliac notches and short iliac wings. The spine shows progressive narrowing of the interpedicular distance from top to bottom (reverse of normal).

**Subfertility is NOT** associated with achondroplasia.

### **Pseudoxanthoma elasticum**

Pseudoxanthoma elasticum is an inherited condition (usually **autosomal recessive**) characterised by an abnormality in **elastic fibres**.

Also there are reports of autosomal dominant inheritance in a minority of cases.

Features:

- 1) **Retinal angioid streaks.**
- 2) **'Plucked chicken skin'** appearance - small yellow papules on the neck, antecubital fossa and axillae.
- 3) **Cardiac: mitral valve prolapse**, increased risk of **IHD**.
- 4) **GI haemorrhage.**

### **Galactosaemia**

Galactosaemia is a rare autosomal recessive condition caused by the **absence** of **galactose-1-phosphate uridyl transferase**. This results in intracellular accumulation of galactose-1-phosphate.

Features:

- **Jaundice**
- **Failure to thrive**
- **Hepatomegaly**
- **Cataracts**
- **Fanconi syndrome**
- **Hypoglycaemia** after exposure to galactose

Diagnosis:

- Urine reducing substances

Management is with a galactose free diet

### Polymerase chain reaction (PCR)

PCR is a molecular genetic investigation technique.

The main advantage of PCR is its **sensitivity**: only **one** strand of sample DNA is needed to detect a particular DNA sequence.

It now has many uses including prenatal diagnosis, detection of mutated oncogenes and diagnosis of infections. PCR is also extensively used in forensics.

Prior to the procedure it is necessary to have two DNA oligonucleotide primers.

These are complimentary to specific DNA sequences at either end of the target DNA.

Initial prep:

- Sample of DNA is added to test tube along with **two DNA primers**.
- A **thermostable DNA polymerase (Taq)** is added.

The following cycle then takes place:

- Mixture is heated to almost boiling point causing denaturing (uncoiling) of DNA.
- Mixture is then allowed to cool: complimentary strands of DNA pair up, as there is an excess of the primer sequences they pair with DNA preferentially.

The above cycle is then repeated, with the amount of **DNA doubling each time**.

### Reverse transcriptase PCR:

- Used to **amplify RNA**.
- **RNA is converted to DNA by reverse transcriptase**.
- Gene expression in the form of **mRNA** (rather than the actual DNA sequence) can therefore be analysed.

### The main action of:

**PCR >>> DNA amplification.**

**Reverse transcriptase PCR >>> RNA amplification.**

**Molecular biology techniques**

The following table shows a very basic summary of molecular biology techniques:

Technique	Description
<b>Southern blotting</b>	Detects <b>DNA</b> .
<b>Northern blotting</b>	Detects <b>RNA</b> .
<b>Western blotting</b>	Detects <b>proteins</b> . Uses gel electrophoresis to separate native proteins by 3-D structure. Examples include the <b>confirmatory</b> HIV test.

**Molecular biology techniques:**

- SNOW (**S**outh - **N**Orth - **W**est): Detect:
- DROP (**D**NNA - **R**NA - **P**rotein)

**Enzyme-linked immunosorbent assay (ELISA):**

- A type of biochemical assay used to detect antigens and antibodies.
- A colour changing enzyme is attached to the antibody if looking for an antigen and to an antigen if looking for an antibody.
- The sample therefore changes colour if the antigen or antibody is detected.
- An example includes the **initial** HIV test.

The most suitable technique to **detect** and **quantify a viral protein** is >> **Western blotting (NOT PCR)**.

A scientist is developing a new test for Bovine spongiform encephalopathy that uses gel electrophoresis to separate native **proteins** by 3-D structure. This is an example of >>> **Western blotting**

### Trinucleotide repeat disorders

Trinucleotide repeat disorders are genetic conditions caused by an abnormal number of repeats (expansions) of a repetitive sequence of three nucleotides.

These expansions are unstable and may enlarge which may lead to **an earlier age of onset in successive generations** - a phenomenon known as "**anticipation**".

In **most** cases, an **increase in the severity of symptoms is also noted**.

The 'classic' definition of anticipation is earlier onset in successive generations. However, in most cases, an increase in the severity of symptoms is also noted. If both options are presented then the second one should be chosen, as this represents the more accepted definition of anticipation.

**"Anticipation"** in trinucleotide repeat disorders = **earlier onset in successive generations**.

Examples: (Note dominance of **neurological** disorders):

- 1) **Fragile X** (CGG)
- 2) **Huntington's** (CAG)
- 3) **Motonic dystrophy** (CTG)
- 4) **Friedreich's** ataxia (GAA) :it is unusual in not demonstrating anticipation
- 5) Spinocerebellar ataxia
- 6) Spinobulbar muscular atrophy
- 7) Dentatorubral pallidoluysian atrophy

### Fragile X

Fragile X is a **trinucleotide repeat** disorder.

Features in males:

- 1) **Mental retardation** and **Learning difficulties**
- 2) **Large low set ears**, long thin face, high arched palate
- 3) **Macroorchidism**
- 4) **Hypotonia**
- 5) **Autism** is more common
- 6) **Mitral valve prolapse**

Features in females (who have one fragile chromosome and one normal X chromosome) range from normal to mild.

Diagnosis:

- Can be made antenatally by **chorionic villus** sampling or amniocentesis
- Analysis of the number of **CGG** repeats using restriction endonuclease digestion and **Southern** blot analysis.

### **Tumour suppressor genes**

Basics:

- Genes which **normally control the cell cycle**.
- Loss of function results in an increased risk of cancer.
- Both alleles must be mutated before cancer occurs.

Examples:

Gene	Associated cancers
p53	Common to many cancers as <b>Li-Fraumeni syndrome</b>
APC	Colorectal cancer
BRCA1	Breast and ovarian cancer
BRCA2	Breast and ovarian cancer
NF1	Neurofibromatosis
Rb	Retinoblastoma
WT1	Wilm's tumour
Multiple tumor suppressor 1 (MTS-1, p16)	Melanoma

<p><b><u>Tumour suppressor genes:</u></b> <b><u>loss</u></b> of function results in an <b>increased</b> risk of cancer.</p> <p><b><u>Oncogenes:</u></b> <b><u>gain</u></b> of function results in an <b>increased</b> risk of cancer.</p>
---

### P53 gene

P53 is a **tumour suppressor gene** located on chromosome **17p**.

It is the most commonly mutated gene in **breast**, **colon** and **lung** cancer.

P53 is thought to play a crucial role in the cell cycle, preventing entry into the S phase until DNA has been checked and repaired. It may also be a key regulator of **apoptosis**.

**Li-Fraumeni syndrome** is a **rare autosomal dominant** disorder characterised by the early onset of a variety of cancers such as **sarcomas** and **breast** cancer. It is caused by **mutation in the p53 gene**.

### Oncogenes

**Oncogenes** are endogenous human deoxyribonucleic acid (DNA) sequences that arise from normal genes called proto-oncogenes.

**Proto-oncogenes** are normally expressed in many cells, particularly during fetal development, and are thought to play an important regulatory role in cell growth and development.

Alterations in the proto-oncogene can activate an oncogene, which produces unregulated gene activity, contributing directly to tumourogenesis.

Oncogene alterations are important causes of:

- Rhabdomyosarcomas (**ras** oncogene)
- Burkitt's lymphoma (**C-myc** is translocated intact from its normal position on chromosome 8 to chromosome 14)
- Neuroblastoma (**N-myc** proto-oncogene is seen in a proportion of patients with poor prognosis).

They should be contrasted with tumour suppressor genes. In this situation, the genes normally down regulate cell growth, and require inactivation to allow malignant growth. Examples include retinoblastoma.

### Down's syndrome: epidemiology and genetics

Risk of Down's syndrome with **increasing maternal age**:

- Risk at **30** years = **1/1000**
- **35** years = **1/350**
- **40** years = **1/100**
- **45** years = **1/30**



One way of remembering this is by starting at <b>1/1,000</b> at <b>30</b> years and then <b>dividing</b> the denominator by <b>3</b> (i.e. 3 times more common) <b>for every extra 5 years of age</b> .
---

**Cytogenetics:**

Mode	% of cases	Risk of recurrence
<b>Non-disjunction</b>	<b>94%</b>	1 in 100 if under mother < 35 years
Robertsonian translocation (usually onto 14)	5%	10-15% if mother is translocation carrier 2.5% if father is translocation carrier
Mosaicism	1%	

The chance of a further child with Down's syndrome is approximately 1 in 100 if the mother is less than 35 years old.

If the trisomy 21 is a result of a translocation the risk is much higher.

**Acute liver failure**

Acute liver failure describes the rapid onset of hepatocellular dysfunction leading to a variety of systemic complications.

Causes:

- 1) **Alcohol**
- 2) **Viral hepatitis** (usually A or B)
- 3) **Paracetamol overdose**
- 4) **Acute fatty liver of pregnancy (AFLP)**

Features:

- Jaundice
- Coagulopathy: raised prothrombin time
- Hypoalbuminaemia
- Hepatic encephalopathy
- Renal failure is common ('hepatorenal syndrome')

Remember that 'liver function tests' do not always accurately reflect the synthetic function of the liver. This is best assessed by looking at the prothrombin time and albumin level.

The main pathological process seen in the hepatocytes of patients with **fulminant hepatitis** is **necrosis** affects the entire acinus (**panacinar necrosis**) resulting in **liver failure**.

This is in contrast to the **apoptosis** seen in patients with **mild** cases of **viral hepatitis**, resulting in the **possibility of regeneration and recovery of hepatocellular function**.

### Membrane receptors

There are **four** main types of membrane receptor:

- 1) Ligand-gated ion channels.
- 2) Tyrosine kinase receptors.
- 3) Guanylate cyclase receptors.
- 4) G protein-coupled receptors.

#### **1) Ligand-gated ion channel receptors:**

- Generally mediate fast responses
- E.g. **nicotinic acetylcholine**, GABA-A & GABA-C, glutamate receptors.

#### **2) Tyrosine kinase receptors:**

- Intrinsic tyrosine kinase: **insulin**, insulin-like growth factor (IGF), epidermal growth factor (EGF).
- Receptor-associated tyrosine kinase: GH, prolactin, IFN, interleukin.

#### **3) Guanylate cyclase receptors:**

- Contain intrinsic enzyme activity
- E.g. atrial natriuretic factor (**ANF**), brain natriuretic peptide (**BNP**) and nitric oxide (**NO**).

#### **4) G protein-coupled receptors:**

- G protein-coupled receptors **span the cell membrane**.

- Generally mediate slow transmission and affect metabolic processes.
- Activated by a wide variety of extracellular signals e.g. Peptide hormones, biogenic amines, lipophilic hormones, light.
- 7-helix membrane-spanning domains.
- Consist of 3 main subunits: alpha, beta and gamma.
- The alpha subunit is linked to GDP. Ligand binding causes conformational changes to receptor, GDP is phosphorylated to GTP, and the alpha subunit is activated.
- G proteins are named according to the alpha subunit ( $G_s$ ,  $G_i$ ,  $G_q$ ).
- e.g. **Adenosine**, muscarinic acetylcholine, **adrenergic receptors**, GABA-B, growth hormone.

	$G_s$	$G_i$	$G_q$
<b>Mechanism</b>	Activates adenylate cyclase → increases cAMP → activates protein kinase A	Inhibits adenylate cyclase → decreases cAMP → inhibits protein kinase A	Activates phospholipase C → splits $PIP_2$ to $IP_3$ & DAG → activates protein kinase C
<b>Examples</b>	<ul style="list-style-type: none"> <li>• Beta-1 receptors (epinephrine, norepinephrine, dobutamine).</li> <li>• Beta-2 receptors (epinephrine, salbutamol).</li> <li>• H2 receptors (histamine).</li> <li>• D1 receptors (dopamine).</li> <li>• V2 receptors (vasopressin).</li> <li>• Receptors for ACTH, LH, FSH, glucagon, PTH, calcitonin, prostaglandins.</li> </ul>	<ul style="list-style-type: none"> <li>• <b>M2</b> receptors (<b>acetylcholine</b>).</li> <li>• Alpha-2 receptors (epinephrine, norepinephrine).</li> <li>• D2 receptors (dopamine).</li> <li>• GABA-B receptor.</li> </ul>	<ul style="list-style-type: none"> <li>• Alpha-1 receptors (epinephrine, norepinephrine).</li> <li>• H1 receptors (histamine).</li> <li>• V1 receptors (vasopressin).</li> <li>• M1, M3 receptors (acetylcholine).</li> </ul>

**Nicotinic Ach receptors >>> Ligand-gated ion channel receptors.**

**Muscarinic Ach receptors >>> G- protein coupled receptors.**

## Second messengers

Overview:

- Many different types
- Allow amplification of external stimulus

	<b>cAMP system</b>	<b>Phosphoinositol system</b>	<b>cGMP system</b>	<b>Tyrosine kinase system</b>
<b>Ligand: Neurotransmitters (Receptor)</b>	Epinephrine ( $\alpha_2$ , $\beta_1$ , $\beta_2$ ) Acetylcholine (M2)	Epinephrine ( $\alpha_1$ ) Acetylcholine (M1, M3)	-	-
<b>Ligand: Hormones</b>	ACTH, ADH, calcitonin, FSH, glucagon, hCG, LH, MSH, PTH, TSH, GHRH*	angiotensin II, GnRH, GHRH*, Oxytocin, TRH	<b>ANP, Nitric oxide (NO)</b>	<b>Insulin, growth hormone (GH), IGF, PDGF</b>
<b>Primary effector</b>	Adenylyl cyclase	Phospholipase C	Guanylate cyclase	Receptor tyrosine kinase
<b>Secondary messenger</b>	cAMP (cyclic adenosine monophosphate)	IP3 (inositol 1,4,5 trisphosphate) and DAG (Diacylglycerol)	cGMP	Protein phosphatase

In **GHRH** and **Adrenaline** >> the **cAMP** pathway is the most important.

### Acute phase reactant proteins

#### Acute phase proteins:

- 1) **CRP**
- 2) **Ferritin**
- 3) **Fibrinogen**
- 4) **Haptoglobin**
- 5) **Complement**
- 6) **Pro-calcitonin**
- 7) **Alpha-1 antitrypsin**
- 8) **Ceruloplasmin**
- 9) **Serum amyloid A**
- 10) **Serum amyloid P** component (It has a more role in mice)

During the acute phase response the **liver decreases the production** of other proteins (sometimes referred to as **negative acute phase proteins**). Examples include:

- 1) **Albumin**
- 2) **Transthyretin** (formerly known as **prealbumin**)
- 3) **Transferrin**
- 4) **Retinol binding protein**
- 5) **Cortisol binding protein**

**NB: ESR is not considered as an acute phase proteins.**

### Erythrocyte sedimentation rate (ESR)

The ESR is a non-specific marker of inflammation and depends on both the size, shape and number of **RBCs** and the concentration of **plasma proteins** such as fibrinogen, alpha2-globulins and gamma globulins.

#### Causes of a high ESR:

- Temporal arteritis
- Myeloma
- Other connective tissue disorders e.g. SLE

- Other malignancies
- Infection
- Other factors which raise ESR: increasing **age**, **female** sex, **anaemia**.

**Causes of a low ESR:**

- **Polycythaemia.**
- **Afibrinogenaemia/hypofibrinogenaemia.**

**Mitochondrial diseases**

Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria which encodes protein components of the respiratory chain and some special types of RNA.

Mitochondrial inheritance has the following characteristics:

- Inheritance is **only** via the **Maternal** line as **the sperm contributes no cytoplasm to the zygote.**
- All children of affected males will not inherit the disease.
- All children of affected females will inherit it.
- Generally encode rare neurological diseases.
- **Poor genotype: phenotype correlation** - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy.

Histology:

- **Muscle biopsy** classically shows '**red, ragged fibres**' due to increased number of mitochondria.

Examples include:

- 1) **Leber's optic atrophy**
- 2) **MELAS syndrome: Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like episodes.**
- 3) **MERRF syndrome: Myoclonus Epilepsy with Red- Ragged Fibres.**
- 4) **Kearns-Sayre syndrome:** onset in patients < 20 years old, external ophthalmoplegia, retinitis pigmentosa. Ptosis may be seen.
- 5) **Sensorineural hearing loss.**

**EX:** A 24-year-old man is investigated for visual loss and is diagnosed as having **Leber's optic atrophy**. So should check **his brothers** and **sister** and sure **his mother** is also affected and is the source of the disease.

### Nitric oxide (NO)

Previously known as endothelium derived relaxation factor, nitric oxide (NO) has emerged as a molecule which is integral to many physiological and pathological processes.

It is formed from **L-arginine** and oxygen by nitric oxide synthetase (NOS).

An inducible form of NOS has been shown to be present in **macrophages**.

Nitric oxide has a **very short half-life (seconds)**, being **inactivated by oxygen free radicals**.

Effects:

- 1) Acts on **Guanylate cyclase receptor** leading to raised **intracellular cGMP** levels and therefore **decreasing Ca<sup>2+</sup> levels**.
- 2) **Vasodilation**, mainly **venodilation**.
- 3) **Inhibits platelet aggregation**.

Nitric oxide > ↑cGMP>>↓Ca<sup>++</sup> >>>> vasodilation + inhibits platelet aggregation

Clinical relevance:

- **Underproduction** of NO is implicated in **hypertrophic pyloric stenosis**.
- **Lack** of NO is thought to promote **atherosclerosis**.
- In sepsis **increased** levels of NO contribute to **septic shock**.
- Organic nitrates (metabolism produces NO) is widely used to treat cardiovascular disease (e.g. angina, heart failure).
- Sildenafil is thought to potentiate the action of NO on penile smooth muscle and is used in the treatment of erectile dysfunctions.

## Puberty

**Failure of menarche by age 16** is a recognised sign of **delayed puberty** and should prompt targeted examination and appropriate investigations.

Both hypogonadotrophic causes such as low weight / malnutrition, and hypergonadotrophic causes such as Turner's syndrome are recognised.

### Recognised signs of delayed puberty in girls include:

- 1) **Menarche has not occurred by age 16.**
- 2) **Absence of pubic hair** by age 14
- 3) **Absence of breast** development by age 14 years
- 4) More than 5 years between the start and completion of breast growth

### Recognised signs of delayed puberty in boys include:

- 1) **No testicular** enlargement by age 14 years
- 2) **Absence of pubic hair** by age 15
- 3) More than 5 years between the start and completion of growth of the genitalia.

## Turner's syndrome

Turner's syndrome is a chromosomal disorder affecting around **1 in 2,500** females.

It is caused by either the presence of **only one sex chromosome (X)** or a deletion of the short arm of one of the X chromosomes.

Turner's syndrome is denoted as **45, XO** or **45, X**.

Features:

- 1) **Short stature.**
- 2) Shield chest, widely spaced nipples.
- 3) **Webbed neck.**
- 4) **Bicuspid aortic valve** (15%), **Coarctation of the aorta** (5-10%)
- 5) **Primary amenorrhoea.**
- 6) Cystic hygroma (often diagnosed prenatally).
- 7) **High-arched palate.**
- 8) Short fourth metacarpal.



- 9) Multiple pigmented naevi.
- 10) Lymphoedema in neonates (especially feet).
- 11) There is also an increased incidence of autoimmune disease (especially **autoimmune thyroiditis**) and **Crohn's disease**.

Turner's syndrome > the most common cardiac defect is bicuspid aortic valve

**EX.** Young female with 1ry amenorrhea + HTN >>>> think of: Turner syndrome or congenital adrenal hyperplasia.

### Noonan's syndrome

Often thought of as the '**male Turner's**', Noonan's syndrome is an **autosomal dominant** condition associated with **a normal karyotype**.

It is thought to be caused by a defect in a gene on chromosome **12**.

As well as features similar to Turner's syndrome (webbed neck, widely-spaced nipples, short stature, pectus carinatum and excavatum), a number of characteristic clinical signs may also be seen:

- 1) Cardiac: **pulmonary valve stenosis**
- 2) **Ptosis**
- 3) **Triangular-shaped face**
- 4) **Low-set ears**
- 5) Coagulation problems: **factor XI deficiency**

### Klinefelter's syndrome

It is a sex chromosome disorder affecting **1:500 - 1:1000** male births.

Typically associated with **karyotype 47, XXY** or XXXYY or XXYY

It involves the loss of Leydig cells and seminiferous tubular dysgenesis.

The rate of chromosomal non dysjunction increases with increasing the **maternal** and **paternal ages**, **each** parent contributing **50%** of the risk.

Around 60% of Klinefelter's does not survive the fetal period.

Features:

- 1) Often **taller** than average

- 2) **Lack of secondary sexual characteristics**
- 3) **Small, firm testes**
- 4) **Infertile**
- 5) **Gynaecomastia** - increased incidence of **breast cancer**
- 6) **Elevated gonadotrophin levels (↑ FSH and LH)**
- 7) With **low testosterone**.
- 8) Bone mineral density is decreased, and they are at increased risk of **osteoporotic fractures**.
- 9) LDL levels may be normal or increased, **low HDL** and **high triglyceride** levels with increased cardiovascular risk and this at least in part may stem from **abnormalities in lipid metabolism**.

Diagnosis is by **chromosomal analysis (Karyotyping)**.

**TTT:**

- Androgen replacement
- Cosmetic correction of gynaecomastia
- Psychosocial counselling.

**EX:** Male pt. with **Colles** fracture after **minor** trauma, **DEXA** T-score **-3**, **depression**, **impotence**, loss of libido, sparse secondary sexual hair, small testis >>>? **Klinefelter's** >>> ttt: **Testosterone** which will improve bone mineralization, good impact on his sexual life and depressive symptoms.

Unfortunately due to late diagnosis of Klinefelter's, a significant number of patients begin testosterone replacement therapy far too late.

### **Kallman's syndrome**

Kallman's syndrome is a recognised cause of delayed puberty secondary to **hypogonadotrophic hypogonadism**.

It is usually inherited as an **X-linked recessive** trait.

Incidence of 1 in 10,000 male.

Kallman's syndrome is thought to be caused by **failure of GnRH-secreting neurons and the olfactory neurones to migrate to the hypothalamus during development**.

The clue given in many questions is **lack of smell (anosmia)** (in **75%** of cases) in a **boy** with **delayed puberty** and an increased association with **cleft lip and palate**.

Kallman's syndrome may arise due to abnormalities of the KAL-1 or KAL-2 gene (encoding anosmin-1 and FGF-1).

Whilst the majority of cases are sporadic, perhaps up to 50% of cases are due to genetic inheritance.

**Fluorescent in situ hybridisation (FISH)**, using a specific chromosomal probe, is currently **the best means** of a genetic diagnosis of this condition.

**MRI brain: Absent olfactory bulbs** in **75%** of MRI scans.

Features:

- **'Delayed puberty'**
- **Hypogonadism: cryptorchidism (undescended testes) in males or primary amenorrhoea in female**
- **Anosmia**
- Sex hormone (Oestrogen in female or Testosterone in male) are **low**.
- LH, FSH levels are **inappropriately low/normal**, (rather than the high concentrations expected with primary gonadal failure).
- Otherwise normal anterior pituitary function (**Normal prolactin**).
- Patients are typically of normal or above average height.
- Cleft lip/palate and visual/ sensorineural hearing defects are also seen in some patients

TTT:

- **Pulsed GnRH therapy** or **gonadotrophin** therapy can be used to restore fertility, or
- **Testosterone** can be used to drive development and restore of secondary sexual characteristics, but won't restore fertility.

**EX:** A 16-year-old male has lack of pubertal development + his testes are undescended and there is only scanty pubic hair. The most likely diagnosis is **Kallman's syndrome**.

**Klinefelter's >>> LH & FSH raised**

**Kallman's >>> LH & FSH low-normal, at least not raised**

**NB: Andropause** is the term for the gradual decrease in serum testosterone concentration with age, but does not occur, usually, until after the age of 50.

With men, gonadal failure occurs typically more slowly than in women at the menopause. Thus a 50-year-old man would not necessarily be expected to show a picture of gonadal failure.

In **ageing** and **primary testicular failure** >>> **LH and FSH are elevated** and **testosterone is low**.

In **hypopituitarism** >>> all are low (Low LH, FSH and Testosterone).

Many men are treated with **gonadotrophin antagonists** (as in cancer prostate) can cause a similar pattern to hypopituitarism.

NB: in **haemochromatosis** also >>> pituitary infiltration >>> Hypo gonadotrophic hypogonadism (all are low) >>> so check serum **ferritin**.

### Prader-Willi syndrome

It is an example of genetic imprinting where the **phenotype depends** on whether the **deletion** occurs on a gene inherited from the mother or father:

- **Prader-Willi syndrome** if gene deleted from **father**
- **Angelman syndrome** if gene deleted from **mother**

#### Deletion of chromosome 15:

- **Prader-Willi** - paternal
- **Angelman syndrome** – maternal

Prader-Willi syndrome is associated with the absence of the active Prader-Willi gene on the long arm of chromosome **15**. This may be due to:

- **Microdeletion of paternal 15q11-13 (70% of cases)**.
- Maternal uniparental disomy of chromosome 15.

The most common genetic cause is >> **Microdeletion of the paternal 15q11-13**

Features:

- Hypotonia during infancy
- Dysmorphic features

- Short stature
- Hypogonadism and infertility
- Learning difficulties
- Childhood obesity
- Behavioural problems in adolescence

### Fragile X syndrome (large ear, large testes)

In addition to moderate to severe **mental retardation**, other characteristics of individuals with Fragile X syndrome may include:

- The face is typically **long and narrow**, with a **high arched palate** and **large ears**.
- **Macroorchidism (large testes)**.
- Prognathism
- **Speech delays**
- Prominent forehead
- Double-jointedness
- Autistic symptoms, and
- Occasional self-mutilation.
- Otitis media, strabismus, and dental problems may be present.

Other common characteristics include:

- Hyper-extensible joints
- Hypotonia, and
- Heart problems, including mitral valve prolapse.

In post pubertal males, **abnormally large testes are a distinctive feature**.

The following can occur in young children:

- **Delayed motor development**
- Hyperactivity
- Behavioural problems
- Toe walking, and
- Occasional seizures.

### Premature ovarian failure

Premature ovarian failure is defined as **the onset of menopausal symptoms** and **elevated gonadotrophin levels (FSH & LH)** before the age of **40** years.

Causes:

- **Idiopathic** - the most common cause
- Chemotherapy
- Autoimmune
- Radiation

Features are similar to those of the normal climacteric but the actual presenting problem may differ.

- 1) **Climacteric symptoms**: hot flushes, night sweats
- 2) **Infertility**
- 3) **Secondary amenorrhoea**
- 4) **Raised FSH, LH** levels with **low Oestradiol**.

**Premature ovarian failure = elevated FSH levels above 30 IU/L** are generally considered **post-menopausal**. Levels above 12 are considered raised in a woman still having periods.

### Positron Emission Tomography (PET)

It is a form of nuclear imaging which uses fluorodeoxyglucose (**FDG**) as the **radiotracer**. This allows a 3D image of **metabolic activity** to be generated using **glucose uptake** as a proxy marker.

The images obtained are then combined with a conventional imaging technique such as CT to decide whether lesions are metabolically active.

Uses:

- Evaluating primary and possible metastatic disease.
- Cardiac PET: not used mainstream currently.

## Cardiovascular physiology

### Left ventricular ejection fraction:

Left ventricular ejection fraction = (stroke volume / end diastolic LV volume) \* 100%

Stroke volume = end diastolic LV volume - end systolic LV volume

### Pulse pressure:

Pulse pressure = Systolic Pressure - Diastolic Pressure

Factors which increase pulse pressure (EX BP= 170/65 mmHg):

- 1) A less compliant aorta (**Reduced aortic compliance**) (this tends to occur with advancing age).
- 2) Increased stroke volume.

## Altitude related disorders

There are **three** main types of altitude related disorders:

Acute mountain sickness (**AMS**), which may progress to high altitude pulmonary edema (**HAPE**) or high altitude cerebral edema (**HACE**).

All three conditions are due to the **chronic hypobaric hypoxia** which develops at high altitudes.

AMS is generally a self-limiting condition. Features of AMS start to occur above **2,500 - 3,000m**, developing gradually **over 6-12 hours** and potentially last a number of days:

- Headache
- Nausea
- Fatigue

### Prevention and treatment of AMS:

- Acute mountain sickness is generally a self-limiting condition
- The risk of AMS may actually be positively correlated to physical fitness.
- Gain altitude at no more than 500 m per day.
- **Acetazolamide** (a carbonic anhydrase inhibitor) is widely used to prevent AMS and has a supporting evidence base.
- The best prevention is **slow acclimatisation**.
- **TTT: descent**.

A minority of people **above 4,000m** go onto develop high altitude pulmonary oedema (HAPE) or high altitude cerebral oedema (HACE), potentially fatal conditions.

- HAPE presents with classical pulmonary oedema features.
- HACE presents with severe headache, profuse vomiting, ataxia, and papilledema.

### Management of HAPE:

- Descent
- Nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V inhibitors >>> All seem to work by reducing systolic pulmonary artery pressure. (NOT Lasix IV).
- Oxygen (high concentration) if available should be initiated firstly especially if with hypoxia

### Management of HACE:

- Descent
- Dexamethasone

### **Pulmonary surfactant**

Surfactant is a mixture of phospholipids, carbohydrates and proteins released by **type 2 pneumocytes**.

The main functioning component is **dipalmitoyl phosphatidylcholine (DPPC)** which **reduces alveolar surface tension**.

Basics:

- First detectable around **28 weeks**.
- As alveoli decrease in size, surfactant concentration is increased, helping prevent the alveoli from collapsing.
- Reduces the muscular force needed to expand the lungs (i.e. decreases the work of breathing).
- Lowers the elastic recoil at low lung volumes and thus helps to prevent the alveoli from collapsing at the end of each expiration

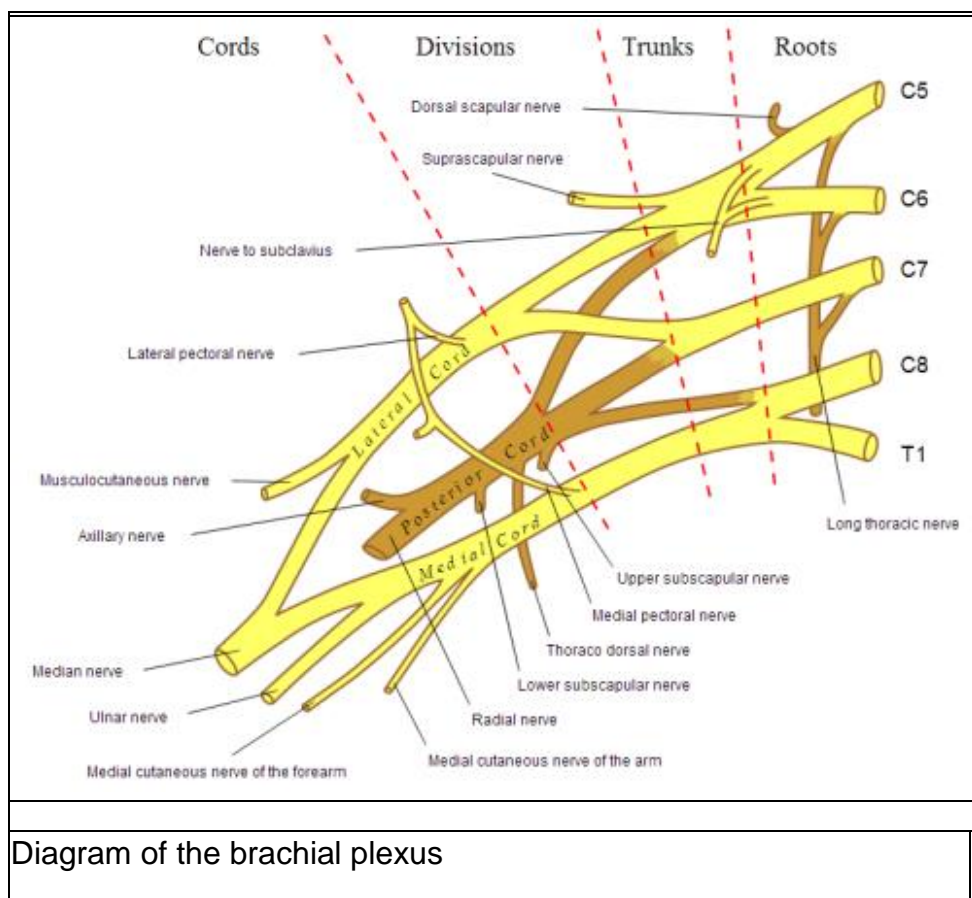


Upper limb anatomy

The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Musculocutaneous nerve (C5-C7)	Elbow flexion (supplies biceps brachii) and supination	Lateral part of the forearm	Isolated injury rare - usually injured as part of brachial plexus injury
<b>Axillary</b> nerve (C5,C6)	<b>Shoulder abduction</b> ( <b>deltoid</b> muscle)	Inferior region of the deltoid muscle	Humeral neck fracture/dislocation  Results in flattened deltoid
Radial nerve (C5-C8)	Extension (forearm, wrist, fingers, thumb)	Small area between the dorsal aspect of the 1st and 2nd metacarpals	Humeral midshaft fracture  Palsy results in wrist drop
Median nerve (C6, C8, T1)	LOAF* muscles  Features depend on the site of the lesion: <ul style="list-style-type: none"> <li>wrist: paralysis of thenar muscles, opponens pollicis</li> <li>elbow: loss of pronation of forearm and weak wrist flexion</li> </ul>	Palmar aspect of lateral 3½ fingers	Wrist lesion → carpal tunnel syndrome

Nerve	Motor	Sensory	Typical mechanism of injury & notes
<b>Ulnar nerve</b> (C8, T1)	<b>Intrinsic</b> hand muscles <b>except LOAF*</b>  Wrist flexion	Medial 1½ fingers	Medial epicondyle fracture  Damage may result in a ' <b>claw hand</b> '
Long thoracic nerve (C5-C7)	<b>Serratus anterior</b>		Often during sport e.g. following a blow to the ribs. Also possible complication of mastectomy  Damage results in a <b>winged scapula</b>



**Erb-Duchenne palsy ('waiter's tip'):**

- Due to damage of the **upper trunk of the brachial plexus (C5, C6)**.
- May be secondary to **shoulder dystocia** during birth.
- The arm hangs by the side and is internally rotated, elbow extended.

**Klumpke injury:**

- Due to damage of the **lower trunk of the brachial plexus (C8, T1)**.
- As above, may be secondary to shoulder dystocia during birth. Also may be caused by a sudden upward jerk of the hand.
- Associated with **Horner's syndrome**.

**\*LOAF muscles:**

- 1) **Lateral 2 lumbricals**
- 2) **Opponens pollicis**
- 3) **Abductor pollicis brevis**
- 4) **Flexor pollicis brevis**

**Radial nerve**

Overview:

- Arises from the posterior cord of the brachial plexus (**C5-8**).

Motor to:

- **Extensor** muscles (forearm, wrist, fingers, thumb).

Sensory to:

- **Dorsal** aspect of **lateral 3 1/2 fingers**.
- However, only small area between the dorsal aspect of the 1st and 2nd metacarpals is unique to the radial nerve.

Patterns of damage:

- **Wrist drop**.
- Sensory loss to small area between the dorsal aspect of the 1st and 2nd metacarpals.

Axillary damage:

- **As above**.
- **Paralysis of triceps**.

## Ulnar nerve

Overview:

- Arises from medial cord of brachial plexus (C8, T1)

Motor to:

- **Ulnar >>> All Intrinsic hand muscles except LOAF\***
- Medial two lumbricals
- ADductor pollicis
- **Interossei**
- Hypothenar muscles: abductor digiti minimi, flexor digiti minimi
- Flexor carpi ulnaris

Sensory to:

- **Medial 1 1/2 fingers (palmar and dorsal aspects)**

## Patterns of damage

### Damage at wrist:

- 1) **'Claw hand'** - hyperextension of the metacarpophalangeal joints and flexion at the distal and proximal interphalangeal joints of the 4th and 5th digits
- 2) Wasting and paralysis of **intrinsic hand muscles (except lateral two lumbricals)**
- 3) Wasting and paralysis of **hypothenar** muscles
- 4) Sensory loss to the medial 1 1/2 fingers (palmar and dorsal aspects)

### Damage at elbow:

- As above (however, **ulnar paradox - clawing** is **more severe** in **distal** lesions).
- Radial deviation of wrist.

## Common peroneal nerve lesion

The **sciatic nerve** divides into the **tibial** and **common peroneal nerves**.

Injury often occurs at the **neck of the fibula**.

The **most characteristic feature** of a common peroneal nerve lesion is **foot drop**.

Other features include:

- 1) **Weakness of foot dorsiflexion.**
- 2) **Weakness of foot eversion.**
- 3) **Weakness of extensor hallucis longus.**
- 4) **Sensory loss** over the **dorsum of the foot** and **the lower lateral part of the leg.**
- 5) **Wasting** of the **anterior tibial** and **peroneal muscles.**

The degree of wasting will depend on **how long** the palsy had been present.

### Foramina of the skull

Below is a brief summary of the major foramina, please see the **Wikipedia** link for a full list (**List of foramina of the human body**).

Foramen	Bone	Vessels	Nerves
Optic canal	Sphenoid	Ophthalmic artery	<b>Optic nerve (II)</b>
Superior orbital fissure	Sphenoid	Superior ophthalmic vein Inferior ophthalmic vein	<b>Oculomotor nerve (III)</b> <b>Trochlear nerve (IV)</b> lacrimal, frontal and nasociliary branches of ophthalmic nerve (V1) Abducent nerve (VI)
Inferior orbital fissure	Sphenoid and maxilla	Inferior ophthalmic veins Infraorbital artery Infraorbital vein	Zygomatic nerve and infraorbital nerve of maxillary nerve (V2) Orbital branches of pterygopalatine ganglion
<b>Foramen rotundum</b>	Sphenoid	-	<b>Maxillary nerve (V2)</b>

Foramen	Bone	Vessels	Nerves
<b>Foramen ovale</b>	Sphenoid	Accessory meningeal artery	<b>Mandibular nerve (V3)</b>
<b>Jugular foramen</b>	Occipital and temporal	Posterior meningeal artery Ascending pharyngeal artery Inferior petrosal sinus Sigmoid sinus Internal jugular vein	Glossopharyngeal nerve ( <b>IX</b> ) Vagus nerve ( <b>X</b> ) Accessory nerve ( <b>XI</b> )

### Renal anatomy

The tables below show the anatomical relations of the kidneys:

#### Right kidney:

Direct contact	Layer of peritoneum in-between
<ul style="list-style-type: none"> <li>- Right suprarenal gland</li> <li>- <b>Duodenum</b></li> <li>- Colon</li> </ul>	<ul style="list-style-type: none"> <li>- Liver</li> <li>- Distal part of small intestine</li> </ul>

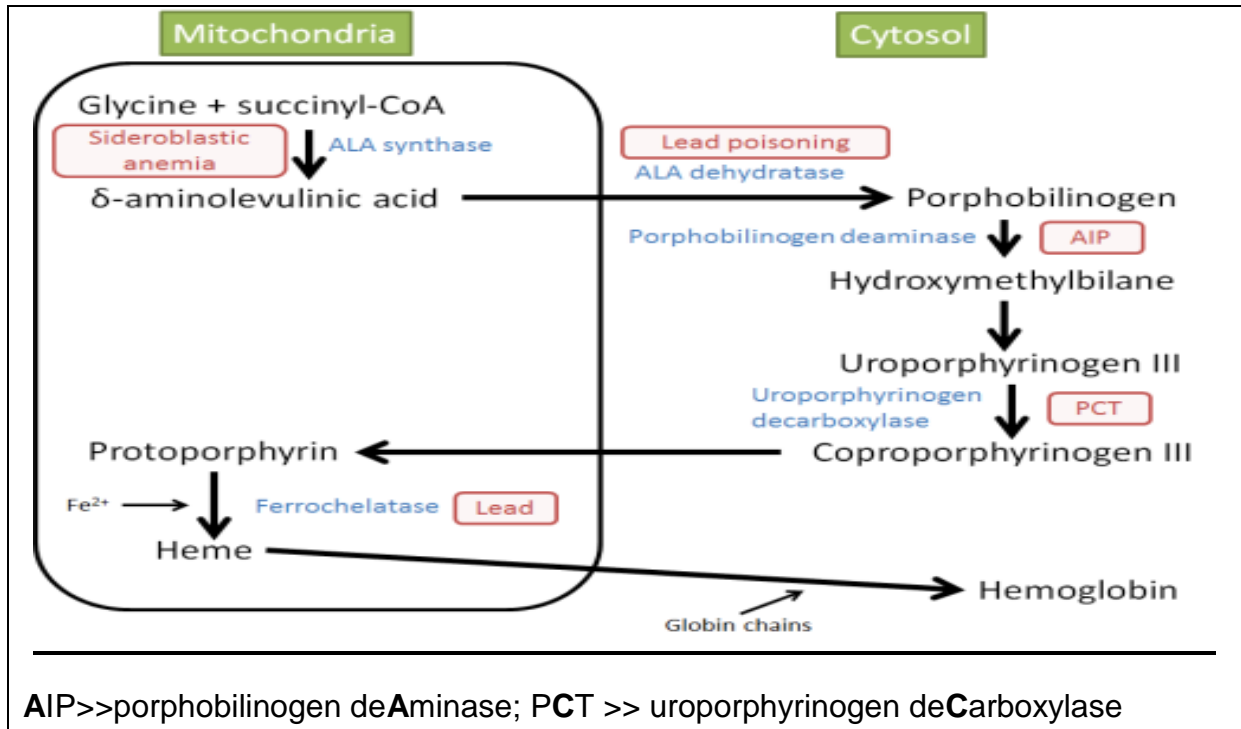
#### Left kidney:

Direct contact	Layer of peritoneum in-between
<ul style="list-style-type: none"> <li>- Left suprarenal gland</li> <li>- <b>Pancreas</b></li> <li>- Colon</li> </ul>	<ul style="list-style-type: none"> <li>- Stomach</li> <li>- Spleen</li> <li>- Distal part of small intestine</li> </ul>

## Porphyrias

Overview:

- Abnormality in enzymes responsible for the **biosynthesis of haem**.
- Results in **overproduction** and **excretion** of intermediate compounds called **porphyrins**.
- May be acute or non-acute.



### Acute intermittent porphyria (AIP):

- It is a **rare Autosomal dominant**.
- **Defect** in RBCs **porphobilinogen (PBG) deaminase**, which is an enzyme involved in the biosynthesis of haem, so increased urinary excretion of the haem precursor **porphobilinogen (PBG)** in urine.
- All attacks of porphyria **increase activity** of **hepatic 5-aminolevulinate (ALA) synthase**.
- **AIP** is caused by **toxic accumulation** of **porphobilinogen (PBG)** and **delta aminolaevulinic acid (DALA)**.
- The relation between these biochemical abnormalities and the neuronal dysfunction which underlies all the features of an acute attack is uncertain.
- **Female (5:1)** and **20-40 year olds** more likely to be affected.

- Only rarely presents before puberty with **90%** of affected individuals remain **asymptomatic throughout their lives**.
- Typically present with **abdominal** and **neuropsychiatric** symptoms (**Neuro-visceral crisis**).
- **Acute abdominal pain and vomiting** are the **commonest** presenting features (**90%**), often associated with **neuropsychiatric** symptoms, ranging from anxiety and depression to fits and frank psychosis.
- Symptoms include **severe neuropathic abdominal pain with peritonism** (85-95%), **vomiting** (50-90%), **paresis** (40-70%) and **seizures** (10-20%).
- Patients feel **normal between attacks**.
- **Hypertension** and **tachycardia** common.
- AIP is also associated with a **mild increase in temperature** and **hyponatraemia (SIADH)**.
- **Urine turns deep red on standing**.
- Photosensitivity is unusual in AIP and patients excrete urinary PBG between and during acute attacks.
- **Raised urinary porphobilinogen (PBG)** greater than **4 times the upper limit** of normal (elevated between attacks and to a greater extent during acute attacks).
- **Raised serum levels of delta aminolaevulinic acid (DALA) and porphobilinogen**.
- Faecal porphyrin excretion is usually normal or slightly increased.
- **Two** procedures have been shown to **decrease** the activity of ALA synthase: **carbohydrate loading** and **parenteral infusion of Haem**.
- **Management includes:**
  - Analgesia - **opiates** (morphine) are often required.
  - **High carbohydrate intake (IV Glucose)**
  - And in severe attacks (**Haematin**) **haem arginate IV infusion: is the ttt of choice** which inhibit haem production and thereby reduce porphyrin synthesis.
  - **Aspirin** and **paracetamol** are safe in porphyria as well as **gabapentin** (used to control seizure activity).
  - Most other anti-epileptics including BDZ (Dormicum) may exacerbate attacks, as well as metoclopramide and domperidone, so **phenothiazines** should be used to control nausea.



- Hypertension and hyponatraemia should be corrected due to the increased risk of seizure.
- Stress, infection, pregnancy, menstruation, OCP, starvation (low carbohydrate intake) and certain drugs may precipitate acute attacks.
- In general, **drugs** that lead to **increased activity of the hepatic P450** system, such as phenobarbital, sulphonamides, **oestrogens**, and **alcohol**, are associated with increased risk of acute attacks.

Drugs which may precipitate attack:	Safe drugs
1) <b>Alcohol</b> 2) <b>Benzodiazepines (BDZ)</b> 3) <b>Barbiturates (Thiopentone)</b> 4) <b>Halothane</b> 5) <b>Oral contraceptive pill</b> 6) <b>Sulphonamides</b> 7) <b>Phenytoin</b>	1) Aspirin 2) Paracetamol 3) Codeine 4) Morphine  5) <b>Chlorpromazine (Largactil)</b> 6) Beta-blockers 7) Penicillin 8) Metformin

**Ibuprofen** is **safe** for use in AIP, but diclofenac should be avoided.

A 43-year-old man presents with known acute intermittent porphyria is brought to the Emergency Department by the police due to an acute psychosis. What is the most suitable drug for sedation? >> **Chlorpromazine (NOT BDZs)**.

Use of **IV glucose during an attack** can lead to more rapid resolution of symptoms, as such that would be the favoured first approach. It will have most impact in shortening the duration and severity of symptoms.

**Phenothiazines** may be used for restlessness, nausea and anxiety, and **beta blockers** have a role in the management of sympathetic activation. **Opiates** can be used as analgesics.

**EX:** A **27-year-old woman** presents to the ER very **agitated**, complaining of **abdominal pain**. This has been her 3<sup>rd</sup> **recurrent** attendance over the past 6 months, and each time there have been no significant findings. Her only medication of note is the **oral contraceptive pill** and **oral antihistaminic**.

On this occasion her **BP is elevated 155/90 mmHg**, her pulse is 92, and her **temperature is 37.8°C**. Her abdomen is **generally tender but soft**, and she has active bowel sounds. She complains of **lower limb weakness**, and she appears to have 4/5 power weakness below the knee. Lab: **serum Na 132 mmol/l**, **mild leucocytosis**.

The most likely diagnosis is >>> **acute intermittent porphyria (AIP)**.

**EX:** A **23-year-old woman** presents to the hospital with a **third** attack of **anxiety, abdominal pain** and **hypertension** in the last six months.

O/E: BP is 150/80 mmHg, pulse is 95 and regular. She has generalised abdominal pain but her abdomen is soft and she has active bowel sounds, Lab: Serum Na 130 mmol/L >>> **acute intermittent porphyria with SIADH**.

**Porphyria cutanea tarda (PCT)** (see pic):

- Most common hepatic porphyria.
- Defect in **uroporphyrinogen decarboxylase**.
- May be caused by hepatocyte damage e.g. excess **alcohol**, oestrogens and iron.
- Classically **photosensitive rash** with bullae, skin fragility on face and dorsal aspect of hands.
- Urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp.
- **TTT:**
  - **Withdrawal** of the precipitant.
  - **Venesection** is effective (450 ml/week) until Hb is 120 g/L.
  - **Chloroquine** may also be effective because it promotes porphyrin excretion.

**Variegate porphyria:**

- Autosomal dominant.
- Defect in **protoporphyrinogen oxidase**.
- **Characterised by raised faecal porphyrins** (copro-porphyrins and proto-porphyrins).
- It is rarely present with acute episode (unlike AIP).

- **The only reported symptom is photosensitive** blistering rash.
- Abdominal and neurological symptoms
- More common in South Africans

### Splenectomy

Following a splenectomy patients are particularly at risk from:

- 1) **Pneumococcus**,
- 2) **Haemophilus**
- 3) **Meningococcal**
- 4) **Capnocytophaga canimorsus** infections (usually from dog bites).

### Vaccination:

- If elective, should be done **2 weeks prior to operation** in order to ensure an optimal antibody response.
- In emergency splenectomy the patient should be immunised as soon as possible after recovery from the operation and before discharge from hospital.
- Unvaccinated patients splenectomised some time earlier should be vaccinated at the first opportunity.
- Vaccination is delayed for at least 6 months after immunosuppressive chemotherapy or radiotherapy during which time prophylactic antibiotics should be given.
- **Annual influenza** vaccination.
- **Pneumococcal** vaccine **every 5 years**.

All adults who have **hyposplenism**, including patients with **SCD**, need:

- 1) Yearly **influenza** vaccine.
- 2) **Pneumococcal** C vaccine, (adults and children over 2 years) repeated every **five** years.
- 3) **Haemophilus influenzae** type b; **if** not already given as part of childhood immunisation.
- 4) **Conjugated meningococcal C vaccine**; **if** not already given as part of childhood immunisation.
- 5) **Meningococcal ACWY vaccine**; **if** travelling to areas with high risk of meningitis.

Although patients with sickle cell disease (SCD) do need the **yearly influenza** vaccination, they also need **five yearly Pneumovax**.

**Antibiotic prophylaxis:**

- **Penicillin V:** unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be continued **for at least 2 years** and at least until the **patient is 16 years of age**, although the majority of patients are usually put on antibiotic prophylaxis **for life**.

**NB:** Penicillin V would protect the splenectomised patient against *Streptococcus pneumoniae* but not *Haemophilus influenzae* due to the production of beta-lactamases by the organism.

**After splenectomy: (5)**

- 1) Influenza vaccination every 1 year.
- 2) Pneumococcal vaccination every 5 years
- 3) Hib Vaccination
- 4) Meningitis Vaccination.
- 5) Penicillin V for life.

**The mortality of post splenectomy septicaemia can be up to 50%.**

**GMC guidance: confidentiality**

For more detailed information >>> [www.gmc-uk.org/guidance](http://www.gmc-uk.org/guidance)

EX: One of your colleagues confides in you that he has just been diagnosed with hepatitis B. He has not told anyone else as he is worried he may lose his job. He is currently working as a general surgeon in the local hospital. You try to persuade him to inform occupational health but he refuses. What is the most appropriate action?  
>>> **Inform your colleague's employing body** (NOT to send an anonymous letter to his employer).

Whilst reviewing a patient's drug card you notice that you prescribed the wrong dose of atenolol when the patient was initially clerked. Instead of 25mg atenolol OD you prescribed 50mg atenolol OD.

She has received the incorrect dose on two occasions.

On examining Mrs Smith you note her blood pressure and pulse are normal.

Mrs Smith has a past history of anxiety and describes herself as a 'worrier'.

What is the most appropriate action? >>> **Apologise to the patient + complete a clinical incident form.**

In this scenario the patient appears to have come to no harm following the error.

This should not however change your approach to the situation.

**The patient should be informed of what has happened, an apology should be made and reassurance** give that there appears to be no ill effects.

By completing a clinical incident form you add to a body of data which may in the long term change to practice.

An entry to your e-portfolio at least shows that you both acknowledge and are willing to learn from the error.

The yellow card system is intended to report side-effects from drugs rather than prescription errors and hence is fairly pointless.

The dose of a drug a patient takes should be based on clinical need rather than a reluctance to acknowledge an error.

It used to be said **that for procedures 'see one, do one, teach one'**.

These days have long gone. Doctors are now expected to show proof of competency before performing procedures alone. If the F2 doctor has never seen one previously so it is not appropriate for him to insert the ascites drain today. The best option is for him to watch you.

If you are going to let the F2 doctor insert the drain you should be honest with the patient about his lack of experience.

Signing him off without seeing him perform the procedure is a very poor option which could result in a GMC referral if found out. It also puts future patients at risk.

Letting him insert the drain today without supervision is again a very poor option as it puts the patient at risk.

Concerns about the **performance of a more senior colleague** are difficult to handle. The most important thing is not to ignore the situation. One of the advantages of **speaking to the medical director** is that he/she may already have

concerns regarding their performance. Your comments may provide further 'evidence' on which action may be taken.

Speaking directly to the locum consultant is a possibility. He may take the attitude that given the concerns of both the medical and nursing staff it is appropriate to discuss his performance with his colleagues. It is however possible that he could become very defensive and try to stonewall you. Filling a clinical incident form would hopefully trigger management to take action but it would take time before any action or decisions are made.

Asking the nurses to put all the poorly or complex patients under a different consultant may seem attractive as it may minimise harm but it does not tackle the underlying problem and puts other patients potentially at risk from an underperforming doctor.

Phoning the local newspaper is unprofessional, unlikely to result in a speedy resolution and will uniformly decrease local confidence in the department.

A 14-year-old girl is admitted to hospital following a ruptured ectopic pregnancy. She comes from a family of Jehovah's Witnesses. Her haemoglobin on admission is 6.9 g/dl. She consents to a blood transfusion but her mother refuses. What is the most appropriate course of action? >> **Give the blood transfusion**

'You should encourage young people to involve their parents in making important decisions, but you should usually abide by any decision they have the capacity to make themselves'

With respect to Jehovah's witnesses:

'You should not make assumptions about the decisions that a Jehovah's Witness patient might make about treatment with blood or blood products. You should ask for and respect their views and answer their questions honestly and to the best of your ability.'

You may also wish to contact the hospital liaison committees established by the Watch Tower Society (the governing body of Jehovah's Witnesses) to support Jehovah's Witnesses faced with treatment decisions involving blood. These committees can advise on current Society policy regarding the acceptability or otherwise of particular blood products. They also keep details of hospitals and doctors who are experienced in 'bloodless' medical procedures.'

A blood transfusion is clearly in the patient's best interests and in the scenario described above may potentially be life-saving. **Whilst a child cannot refuse treatment they are able to provide consent. Giving the blood transfusion** is therefore both clinically and ethically the right course of action.

Not giving the blood transfusion not only fails to respect the patient's wishes but also causes potential harm.

**Managing young diabetic patients** may be frustrating but needs to be approached in an empathetic manner. **Taking time to explore** why her control is so bad is the best response in this scenario. The GP should hopefully have a long term relationship with the patient and may be in a position to address these problems.

Taking no action ignores the problem. Trying to scare her by showing her patients with complications is a poor option not least because it fails to respect the privacy of the other patients.

Telling her she is wasting NHS resources is uncaring and unprofessional.

Telling her not to turn up at hospital again is indefensible from an ethical and medicolegal perspective.

EX: A 68-year-old man is admitted with hematemesis. A gastroscopy performed as an inpatient shows a carcinoma which is confirmed on biopsy. Who is the most appropriate person to inform the patient of the diagnosis? >> **The consultant in-charge of his care.**

One of the key aims of the entrance exam is to assess a doctor's ability to act in a compassionate and empathetic way. Many of you may recall incidences of patients being told about a cancer diagnosis in inappropriate circumstances.

The most appropriate person to inform the patient is **the consultant in this scenario**. He/she is currently in charge of their care and will be best placed to answer questions about management and prognosis. The F2 doctor will be less able to do this but will at least be known to the patient.

The doctor who performed the gastroscopy is unlikely to know the patient apart from their brief meeting prior to the procedure. Asking the GP to tell the patient is a 'cop-out' on a number of levels. Firstly the patient may feel that the hospital team 'could not be bothered' to tell him themselves. Secondly it results in an unnecessary delay and thirdly the GP may not be best placed to give information on management and prognosis.

Telling the next-of-kin is the worst option as it breaks confidentiality.

EX: You are a ST1 doctor on a medical ward. It is 5:15pm and you were scheduled to finish your day 15 minutes ago. Today you're particularly keen to leave as it is your wife's birthday and you've arranged a night out. One of the staff nurses bleeps you as Mr Jones, one of your patients, has become drowsy. He was admitted two days ago to your ward with an exacerbation of COPD. What is the most appropriate course of action? >>> **Go and assess the patient yourself.**

This question is mainly about professionalism and '**putting the patient first**'.

The most appropriate response is to **go and assess the patient yourself**. You are most likely to know their history and it is possible that the on-call doctor will be delayed in reaching the ward due to other patients.

**The next best option is to bleep the on-call doctor yourself.** This allows for a proper hand-over, which would not happen if you asked the nurse to bleep the on-call doctor.

Filling in a clinical incident form as you were bleeped after hours is not appropriate.

The worst response would be to ask the nurse to instigate medical treatment without first assessing the patient. This is clearly dangerous.

EX: You are a ST1 doctor working on a medical ward. You are struggling to cope with the workload and often leave the ward late. Who is the most appropriate action to take? >>> **Speak to your consultant.**

**Speaking to your consultant** is the first action to take in this scenario. They are best placed to be able to take action to try and amend the situation. As the consultant is ultimately responsible for patient care they also have a right to know if you are struggling to cope as this may affect patient care.

The medical director may also be able to assist but would end up speaking to the consultant and hence is not the first choice.

Arriving early may seem an option but does not ultimately address the cause of the problem.

Taking time off sick is the worst option - it doesn't address the problem and is unprofessional.

EX: You are caring for a local cardiology consultant's father who has been admitted following a myocardial infarction. He bleeps you from the switchboard and asks how his father is doing. You recognise his voice on the phone. What is the most appropriate response? >>> **Ask permission from his father then give relevant details.**

The main nub of this question relates to **confidentiality**. **You cannot give details over the phone to anyone, even his son, without the patient's express permission.** Whilst it may be presumed that this is what the patient would want it is impossible to be sure of the family dynamics.

If the patient has given permission and you are sure you are speaking to the son then giving relevant details is the best option.



Asking the consultant to come to meet him face-to-face in as an option but may not be necessary if the previous conditions are met.

Saying he is 'doing fine' is unlikely to satisfy a consultant cardiologist.

Giving details without first getting permission from the patient is breaking confidentiality, however well intentioned.

Involving a relative in the management of a patient is inappropriate and the worst option.

### **Menstrual cycle**

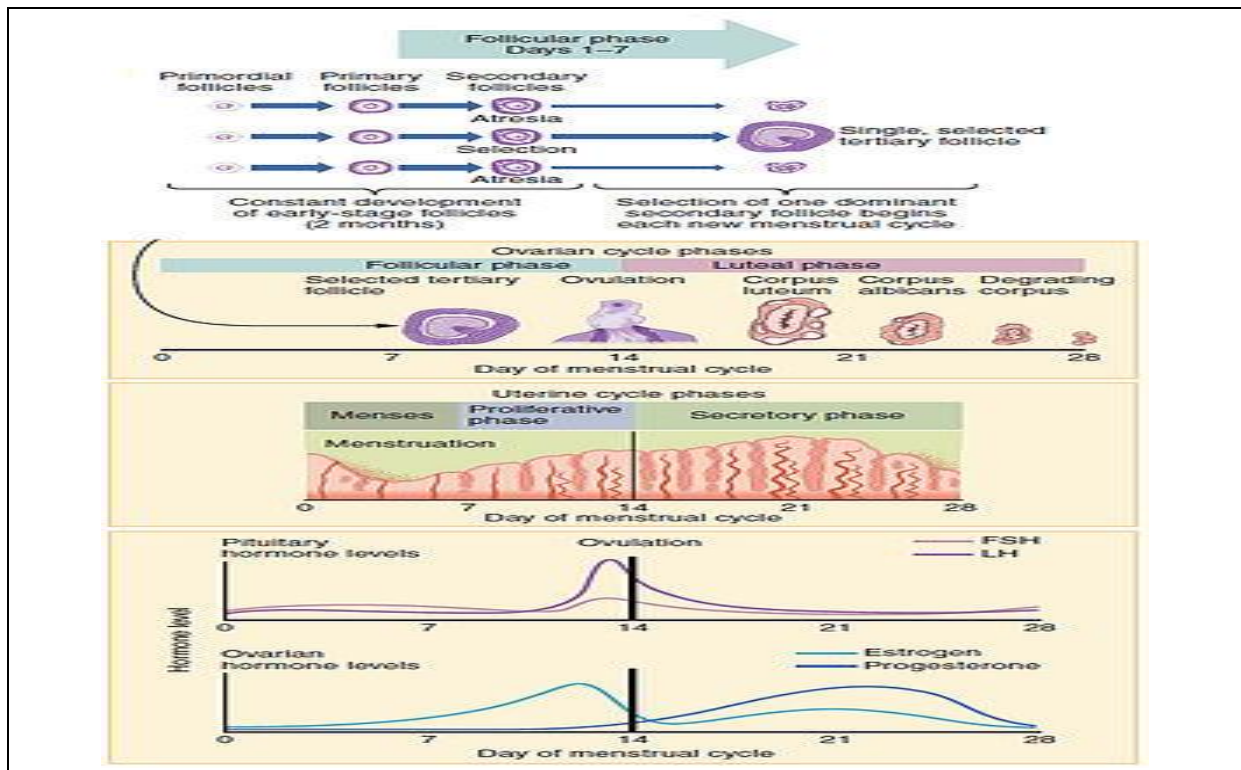
The menstrual cycle may be divided into the following phases:

	<b>Days</b>
<b>Menstruation</b>	1-4
<b>Follicular phase (proliferative phase)</b>	5-13
<b>Ovulation</b>	14
<b>Luteal phase (secretory phase)</b>	15-28

Further details are given in the table below:

	<b>Follicular phase (proliferative phase)</b>	<b>Luteal phase (secretory phase)</b>
<b>Ovarian histology</b>	A number of follicles develop.  One follicle will become dominant around the mid-follicular phase	Corpus luteum

	<b>Follicular phase (proliferative phase)</b>	<b>Luteal phase (secretory phase)</b>
<b>Endometrial histology</b>	Proliferation of endometrium	Endometrium changes to secretory lining under influence of progesterone
<b>Hormones</b>	<p>A rise in <b>FSH</b> results in the development of follicles which in turn secrete oestradiol.</p> <p>When the egg has matured, it secretes <b>enough oestradiol</b> to trigger the acute release of <b>LH</b> &gt; &gt;&gt; <b>LH surge</b> &gt;&gt;&gt; This in turn leads to <b>ovulation</b>.</p>	<p><b>Progesterone</b> secreted by <b>corpus luteum</b> rises through the luteal phase.</p> <p>If fertilisation does not occur the corpus luteum will <b>degenerate</b> and progesterone levels fall.</p> <p>Oestradiol levels also rise again during the luteal phase.</p>
<b>Cervical mucus</b>	<p>Following menstruation the mucus is thick and forms a plug across the external os.</p> <p>Just prior to ovulation the mucus becomes clear, acellular, low viscosity. It also becomes 'stretchy' - a quality termed <b>spinnbarkeit</b></p>	Under the influence of progesterone it becomes thick, scant, and tacky
<b>Basal body temperature</b>	Falls prior to ovulation due to the influence of oestradiol	Rises following ovulation in response to higher progesterone levels



## Energy from food

The amount of energy a food product contains is expressed in calories (kcal).

The amount of energy that may be derived from **1 gram** of food is as follows:

- Carbohydrates: **4 kcal**
- Protein: **4 kcal**
- **Fat: 9 kcal**

In simple terms, per unit weight, fats contain twice as many calories as protein or carbohydrates.

## Leukotrienes

Function:

- Mediators of inflammation and allergic reactions
- Cause **bronchoconstriction, mucous production**
- **Increase vascular permeability, attract leukocytes**
- Leukotriene D4 has been identified as the SRS-A (slow reacting substance of anaphylaxis)

Production:

- **Secreted by leukocytes**
- Formed **from arachidonic acid** by action of lipoxygenase

It is thought that the **NSAID induced bronchospasm** in **asthmatics** is secondary to the express production of leukotrienes due to the inhibition of prostaglandin synthetase.

### Endothelin

Endothelin is a potent, long-acting **vasoconstrictor** and **bronchoconstrictor**.

It is secreted initially as a prohormone by the **vascular endothelium** and later converted to ET-1 by the action of endothelin converting enzyme.

It acts via interaction with a G-protein linked to phospholipase C leading to calcium release.

Endothelin is thought to be important in the pathogenesis of many diseases including primary pulmonary hypertension (endothelin antagonists are now used), cardiac failure, hepatorenal syndrome and Raynaud's.

#### Promotes release:

- 1) **Angiotensin II**
- 2) **ADH**
- 3) **Hypoxia**
- 4) **Mechanical shearing forces**

#### Inhibits release:

- 1) **Nitric oxide**
- 2) **Prostacyclin**

#### Raised levels in:

- MI
- Heart failure
- ARF
- Asthma
- Primary pulmonary hypertension

**Fluid therapy**

The prescription of intravenous fluids is one of the most common tasks that junior doctors need to do. The typical daily requirement is:

- **1.5 ml/kg/hr. fluid** - for a **80kg** man around 2-3 litres/day
- 70-150mmol sodium
- 40-70mmol potassium

This is why the typical regime prescribed for patients is

- **1 litre 5% dextrose** with **20mmol potassium** over 8 hours
- **1 litre 0.9% normal saline** with **20mmol potassium** over 8 hours
- **1 litre 5% dextrose** with **20mmol potassium** over 8 hours

The amount of fluid patients require obviously varies according to their recent and past medical history.

For example a patient who is post-op and is having significant losses from drains will require more fluid whereas a patient with heart failure should be given less fluid to avoid precipitating pulmonary oedema.

The table below shows the electrolyte concentrations (in millimoles/litre) of plasma and the most commonly used fluids:

	Na <sup>+</sup>	Cl <sup>-</sup>	K <sup>+</sup>	HCO <sub>3</sub> <sup>-</sup>	Ca <sup>2+</sup>
<b>Plasma</b>	135-145	98-105	3.5-5	22-28	2.3-2.6
<b>0.9% normal saline</b>	150	150	-	-	-
<b>5% dextrose</b>	-	-	-	-	-
<b>Hartmann's solution</b>	131	111	5	29	2

Understanding sodium requirements is important especially when maintenance intravenous fluid prescriptions are required.

Daily maintenance requirements vary between individuals and the clinical situation, but for a **70 kg male** the generally accepted requirements per day are:

- **2.5-3.0L water**
- **120-140 mmol sodium (~2 mmol/kg)**
- **70 mmol potassium (~1 mmol/kg)**

**Hartmann's solution** contains **131 mmol Na per litre**,

**Normal saline** has **150 mmol/L** and

**Dextrose saline** has **30 mmol/L**.

Q: What is their daily requirement of salt? >>>> **6 gm/day**.

The daily sodium requirement is **70-150mmol**. We can convert this **to mg** by **multiplying by 58.5** (molecular weight of **sodium** is approximately **23**, **chloride** is **35.5**).

So, 70-150mmol = 4095 - 8775mg = 4 - 8.5g. The nearest answer to this is **6g**.

Secondly, this figure ties in with the governments recommended **oral salt intake of 6g/day**.

## Macroglossia

Causes:

- 1) **Acromegaly.**
- 2) **Hypothyroidism.**
- 3) **Amyloidosis.**
- 4) **Duchenne muscular dystrophy.**
- 5) **Mucopolysaccharidosis (e.g. Hurler syndrome).**
- 6) Patients with **Down's syndrome** are now thought to have apparent macroglossia due to a combination of mid-face hypoplasia and hypotonia

## Amyloidosis

It is characterized by **extracellular** deposition of **fibrous protein** in various tissues and organs.

It may be **primary** or **secondary associated** with other chronic diseases like myeloma or rheumatoid arthritis.

Two major types of protein are deposited in tissues:

- 1) Protein light chain (AL) in **primary** amyloidosis and myeloma-associated amyloidosis.
- 2) Non-immunoglobulin protein (AA) in **secondary** amyloidosis usually associated with chronic diseases such as TB, Bronchiectasis, osteomyelitis, rheumatoid arthritis, FMF and Hodgkin's disease.

Symptoms and signs depend on the organ involved.

- **Nephrotic syndrome** is a common mode of presentation.
- **Cardiac** involvement: cardiomegaly, CHF and arrhythmia.
- **Hepatic** amyloid: hepatomegaly and hepatosplenomegaly.
- **Other** organs: lung, thyroid, skin, GIT, tongue, adrenals and LNs.

**Diagnosis:** demonstration of **amyloid fibrils** by **Congo red staining** under **polarised** light microscopy, **abdominal subcutaneous fat pad aspirate** or **rectal submucosal** biopsy are often performed to reach a final diagnosis.

## Clubbing

The causes of clubbing may be divided into cardiac, respiratory and other.

### 1) Cardiac causes:

- 1) **Cyanotic** congenital heart disease (**Fallot's, TGA**)
- 2) Bacterial endocarditis
- 3) Atrial myxoma

### 2) Respiratory causes:

- 1) Pyogenic conditions: **cystic fibrosis**, bronchiectasis, abscess, empyema.
- 2) TB.
- 3) Asbestosis, mesothelioma.
- 4) Fibrosing alveolitis.
- 5) Lung cancer.

**3) Other causes:**

- 1) **IBD: Crohn's**, to a lesser extent UC
- 2) **Cirrhosis, primary biliary cirrhosis**
- 3) **Graves' disease (thyroid acropachy)**
- 4) Rare: **Whipple's** disease

**Valsalva manoeuvre**

The Valsalva manoeuvre describes a **forced expiration against a closed glottis**. This leads to **increased intra-thoracic pressure** which in turn has a number of effects on the cardiovascular system.

**Uses:**

- 1) To terminate an episode of supraventricular tachycardia
- 2) Normalizing middle-ear pressures

**Stages of the Valsalva manoeuvre:**

- 1. **Increased intrathoracic pressure.**
- 2. Resultant increase in venous and right atrial pressure **reduces venous return.**
- 3. The reduced preload leads to a **fall in the cardiac output** (Frank-Starling mechanism).
- 4. When the pressure is released there is a further slight fall in cardiac output due to increased aortic volume.
- 5. Return of normal cardiac output.

**Fitness to fly**

The **Civil Aviation Authority (CAA)** has issued guidelines on air travel for people with medical conditions; please see the link. [www.caa.co.uk](http://www.caa.co.uk)

**Cardiovascular disease:**

- Unstable angina, uncontrolled hypertension, uncontrolled cardiac arrhythmia, decompensated heart failure, severe symptomatic valvular disease: should not fly.
- Uncomplicated myocardial infarction: may fly after 7-10 days.



- Complicated myocardial infarction: after 4-6 weeks.
- Coronary artery bypass graft: after 10-14 days.
- Percutaneous coronary intervention: after 5 days.

### **Respiratory disease:**

- Pneumonia: should be 'clinically improved with no residual infection'.
- Pneumothorax: absolute contraindication, the CAA suggest patients may travel 2 weeks after successful drainage if there is no residual air. The British Thoracic Society used to recommend not travelling by air for a period of 6 weeks but this has now been changed to 1 week post check x-ray.

### **Pregnancy:**

- Most airlines do **not allow** travel **after 36 weeks** for a single pregnancy and **after 32 weeks** for a **multiple** pregnancy.
- Most airlines require a **certificate after 28 weeks** confirming that the pregnancy is progressing normally.

### **Surgery:**

- Travel should be avoided for 10 days following abdominal surgery
- Laparoscopic surgery: after 24 hours
- Colonoscopy: after 24 hours
- Following the application of a **plaster cast**, the majority of airlines restrict flying for **24 hours** on flights of less than 2 hours or **48 hours** for longer flights this is due to the fact that air may be trapped beneath the cast.

### **Haematological disorders:**

- Patients with a haemoglobin of greater than **8 g/dl** may travel without problems (assuming there is no coexisting condition such as cardiovascular or respiratory disease).

Vitamin deficiency

Vitamin	Chemical name	Deficiency state
A	Retinoids	Night-blindness (nyctalopia)
B1	Thiamine	Beriberi: <ul style="list-style-type: none"> <li>• Polyneuropathy, Wernicke-Korsakoff syndrome</li> <li>• Heart failure</li> </ul>
B3	Niacin (Nicotinic acid)	Pellagra: <ul style="list-style-type: none"> <li>• Dermatitis</li> <li>• Diarrhoea</li> <li>• Dementia</li> </ul>
B6	Pyridoxine	Anaemia, irritability, seizures
B7	Biotin	Dermatitis, seborrhoea
B9	Folic acid	Megaloblastic anaemia, deficiency during pregnancy - neural tube defects
B12	Cyanocobalamin	Megaloblastic anaemia, peripheral neuropathy
C	Ascorbic acid	Scurvy: Gingivitis and bleeding
D	Ergocalciferol, cholecalciferol	Rickets, osteomalacia
E	Tocopherol, tocotrienol	Mild haemolytic anaemia in newborn infants, ataxia, peripheral neuropathy
K	Naphthoquinone	Haemorrhagic disease of the newborn, bleeding diathesis

The best source of Vit. D is **Cod liver oil**, it provides about 1,300 IU /15 ml serving.

### Vitamin C (ascorbic acid)

Vitamin C is a water soluble vitamin.

Functions:

- Antioxidant.
- Collagen synthesis: acts as a cofactor for enzymes that are required for the hydroxylation proline and lysine in the synthesis of collagen.
- Facilitates iron absorption.
- Cofactor for norepinephrine synthesis.

Vitamin C deficiency (**scurvy**) leads to defective synthesis of collagen resulting in capillary fragility (bleeding tendency) and poor wound healing.

Features vitamin C deficiency:

- General malaise.
- **Gingivitis**, loose teeth.
- Bleeding from gums, haematuria, and epistaxis.
- Poor wound healing.

### Vitamin B12 deficiency

Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system.

It is **absorbed after binding to intrinsic factor I.F.** (secreted from **parietal cells** in the stomach) and is **actively absorbed in the terminal ileum**.

A **small** amount of vitamin B12 is **passively** absorbed **without being bound** to intrinsic factor.

Vitamin B12 >>>> is **actively** absorbed in the **terminal ileum by IF**.

Causes of vitamin B12 deficiency:

- 1) Pernicious anaemia
- 2) Post gastrectomy
- 3) Poor diet
- 4) Disorders of terminal ileum (site of absorption): Crohn's, blind-loop etc

Features of vitamin B12 deficiency:

- 1) Macrocytic anaemia
- 2) Sore tongue and mouth
- 3) Neuropsychiatric symptoms: e.g. Ataxia and Mood disturbances

Management:

- If no neurological involvement **1 mg of IM Hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months.**
- If a patient is also deficient in folic acid then it is important to **treat the B12 deficiency first** to avoid precipitating subacute combined degeneration (SCD) of the cord.

### Folate metabolism

The best source of food for folic acid >>>> Liver, green vegetables and nuts.

Drugs which interfere with metabolism:

- Trimethoprim
- Methotrexate
- Pyrimethamine

Drugs which can reduce absorption:

- Phenytoin

### Zinc deficiency

Features:

- 1) **Perioral dermatitis: red, crusted lesions**
- 2) **Acrodermatitis**
- 3) **Alopecia**
- 4) **Short stature (Dwarfism)**
- 5) Hypogonadism
- 6) **Hepatosplenomegaly**
- 7) **Geophagia** (ingesting clay/soil)
- 8) Cognitive impairment (mental lethargy)

**NB**: Zn deficiency is associated with **adverse pregnancy outcomes**.

**NB**: Zn supplementation has also been shown to improve neuropsychological function in Chinese children.

**EX**: A 25-year-old female presents with **red crusted** lesions **around the mouth** and **finger pulps** three months after having had **small bowel resection** for **Crohn's** disease.

What is the most likely cause of her skin condition >> **Zinc deficiency**.

### Pellagra

It is characterized by **4Ds: Dementia, Diarrhoea, Dermatitis** and **Death**.

The rash is photosensitive and normally affects the face, neck and forearm.

It is rare and can be **primary** or **secondary**.

**Primary** causes include **niacin** or tryptophan (precursor of niacin) deficiency.

**Secondary** caused include:

- **Carcinoid syndrome**, as the tumour cells convert tryptophan to serotonin, therefore reducing endogenous niacin production.
- **Chronic alcoholism**.
- Anorexia nervosa.
- GIT TB.
- HIV.

Patients usually develop **right-sided valvular disease** >>> Echo: **tricuspid regurgitation** and **pulmonary stenosis**.

**Classification of haemorrhage:**

Parameter	I	II	III	IV
Blood loss (ml)	<750	750-1500	1500-2000	>2000
Blood loss (%)	<15%	15-30%	30-40%	>40%
Pulse rate (beats/min)	<100	>100	>120	>140
Blood pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate (breaths/min)	14-20	20-30	30-40	>35
Urine output (ml/hour)	>30	20-30	5-15	Negligible
CNS symptoms	Normal	Anxious	Confused	Lethargic

**Malignant hyperpyrexia (MH)**

Malignant hyperpyrexia (MH) is characterised by increased temperature and muscle rigidity **during anaesthesia**, which results from abnormal skeletal muscle contraction and increased metabolism.

The predisposing gene is thought to be on **chromosome 19**, close to the gene for the ryanodine/dihydropyridine receptor complex.

Known triggering agents include the volatile anaesthetic agents and **suxamethonium**. Patients show different sensitivity to the triggering agents and the reaction can be delayed by several hours.

**Intravenous dantrolene (up to 10 mg/kg)** is the **only available specific ttt** and care must be taken when administering as **the solution has a pH of 9-10**.

The **prognosis** of malignant hyperpyrexia is **good** when the appropriate treatment is instigated early, **mortality** being **less than 5%** (prior to dantrolene the mortality was 80%).

Serum creatine kinase elevation and myoglobinuria are **suggestive** but **not diagnostic** of MH. Myoglobin and creatine kinase are both known to increase after giving suxamethonium to normal patients.

Contracture tests using caffeine and halothane are the investigations of choice.

Muscle **biopsies** may appear histologically **normal**.

### Hiccup

Hiccup is caused by frequent or **rhythmic clonic contraction** of the **diaphragm**.

When prolonged, other causes should be considered including:

- **CNS** disease - **posterior fossa tumour**, brain injury, encephalitis
- **Phrenic nerve** or **diaphragm irritation** - tumour, pleurisy, pneumonia, intrathoracic adenopathy, pericarditis, GERD.
- **Systemic** causes include **alcohol** intoxication and **uraemia**.
- **Other** causes include foreign body or insect in the ear. In infants it may be associated with apnoea or hyperventilation.

Folk remedies include aerophagia, breath holding, pharyngeal stimulation, distraction.

Haloperidol, metoclopramide and several anaesthetic agents are also said to work.

#### Levels:

- The **carotid artery bifurcates** at **C4**.
- The **manubriosternal joint (angle of Louis)** lies at the level of the **T4/5 intervertebral disk**.
- The **IVC** opening in the diaphragm lies at **T8**.
- The **oesophageal** opening of the diaphragm lies at **T10**.
- The **aortic** opening is at **T12**.

"وما توفيقي الا بالله"